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Reference ranges

End session

Paroxysmal nocturnal haemoglobinuria



Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired disorder leading to haemolysis (mainly intravascular) of haematological cells. It is thought to be caused by increased sensitivity of cell membranes to complement (see below) due to a lack of glycoprotein glycosyl-phosphatidylinositol (GPI). Patients are more prone to venous thrombosis

Pathophysiology

- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane
- complement-regulating surface proteins, e.g. decay-accelerating factor (DAF), are not properly bound to the cell membrane due a lack of GPI
- thrombosis is thought to be caused by a lack of CD59 on platelet membranes predisposing to platelet aggregation

Features

- haemolytic anaemia
- red blood cells, white blood cells, platelets or stem cells may be affected therefore pancytopenia may be present
- haemoglobinuria: classically dark-coloured urine in the morning (although has been shown to occur throughout the day)
- thrombosis e.g. Budd-Chiari syndrome
- aplastic anaemia may develop in some patients

Diagnosis

- flow cytometry of blood to detect low levels of CD59 and CD55 has now replaced Ham's test as the gold standard investigation in PNH
- Ham's test: acid-induced haemolysis (normal red cells would not)

Management

- blood product replacement
- anticoagulation
- eculizumab, a monoclonal antibody directed against terminal protein C5, is currently being trialled and is showing promise in reducing intravascular haemolysis
- stem cell transplantation

[Back to top](#)

VISIT...

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Monoclonal IgM paraprotein band, hyperviscosity syndrome in a question is most likely to indicate:

Myelofibrosis

Overview

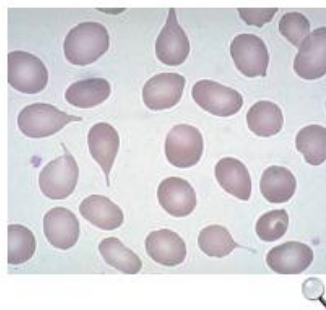
- a myeloproliferative disorder
- thought to be caused by hyperplasia of abnormal megakaryocytes
- the resultant release of platelet derived growth factor is thought to stimulate fibroblasts
- haematopoiesis develops in the liver and spleen

Features

- e.g. elderly person with symptoms of anaemia e.g. fatigue (the most common presenting symptom)
- massive splenomegaly
- hypermetabolic symptoms: weight loss, night sweats etc

Laboratory findings

- anaemia
- high WBC and platelet count early in the disease
- 'tear-drop' poikilocytes on blood film
- unobtainable bone marrow biopsy - 'dry tap' therefore trephine biopsy needed
- high urate and LDH (reflect increased cell turnover)



Blood film showing the typical 'tear-drop' poikilocytes of myelofibrosis

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Back to top

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Features

- 88

Close

Notes (1/2)

Notes (1/2)

Notes (1/1)

Tranexamic acid

Tranexamic acid is a synthetic derivative of lysine. Its primary mode of action is as an antifibrinolytic that reversibly binds to lysine receptor sites on plasminogen or plasmin. This prevents plasmin from binding to and degrading fibrin.

Tranexamic acid is most commonly prescribed to help treat menorrhagia.

The role of tranexamic acid in trauma was investigated in the CRASH 2 trial and has been shown to be of benefit in bleeding trauma when administered in the first 3 hours.

There is also ongoing research looking at the role of tranexamic acid in traumatic brain injury.

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Close

Tranexamic acid is a synthetic derivative of lysine. Its primary mode of action is as an antifibrinolytic that reversibly binds to lysine receptor sites on plasminogen or plasmin. This prevents plasmin from binding to and degrading fibrin.

[Notes](#) (1/1)

Monoclonal IgM paraprotein band, hyperviscosity syndrome - Waldenstrom's macroglobulinaemia

[Notes](#) (1/2)

Tear drop shaped red blood cells - myelofibrosis

[Notes](#) (1/2)

👎 Less relevant ➔

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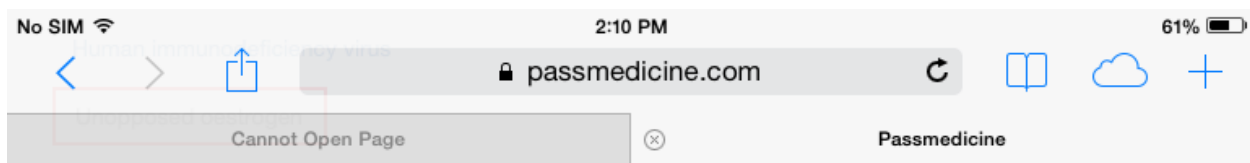


T









High parity

Early menarche

Tamoxifen

Quick comparison: Risk factors: female cancers

Early menarche

- breast cancer
- endometrial cancer
- ovarian cancer

Unopposed oestrogen

- endometrial cancer

👍 Relevant to my revision >

👎 Less relevant >

Breast cancer: risk factors

Predisposing factors

- BRCA genes - 40% lifetime risk of breast/ovarian cancer
- 1st degree relative premenopausal relative with breast cancer (e.g. mother)
- nulliparity, 1st pregnancy > 30 yrs (twice risk of women having 1st child < 25 yrs)
- early menarche, late menopause
- hormone replacement therapy(relative risk increase * 1.023/year of use), combined oral contraceptive use
- past breast cancer
- not breast feeding
- ionising radiation
- p53 gene mutations
- obesity
- previous surgery for benign disease (?more follow-up, scar hides lump)





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Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is caused by a monoclonal proliferation of well-differentiated lymphocytes which are almost always B-cells (99%)

Features

- often none
- constitutional: anorexia, weight loss
- bleeding, infections
- lymphadenopathy more marked than CML

Complications

- hypogammaglobulinaemia leading to recurrent infections
- warm autoimmune haemolytic anaemia in 10-15% of patients
- transformation to high-grade lymphoma (Richter's transformation)

Investigations

- blood film: smudge cells (also known as smear cells)
- immunophenotyping

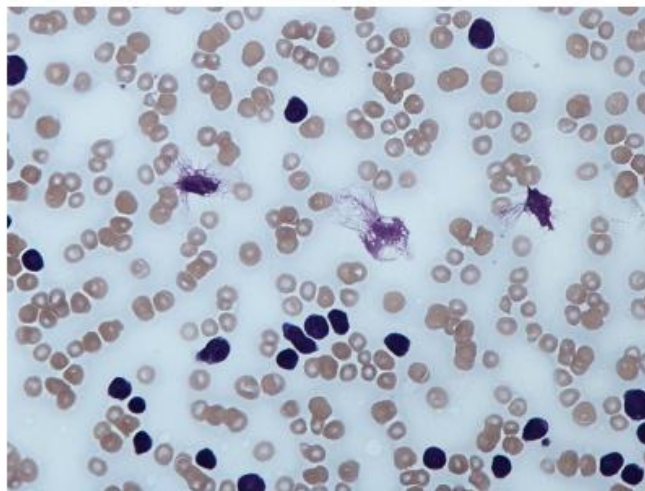


Image sourced from Wikipedia

Peripheral blood film showing smudge B cells

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Cryoglobulinaemia



Question

Immunoglobulins which undergo reversible precipitation at 4 deg C, dissolve when warmed to 37 deg C. One-third of cases are idiopathic

Which one

Non-sp

Selecti

Opioid-

Binds t

Blocks

Promot

Three types

- type I (25%): monoclonal
- type II (25%): mixed monoclonal and polyclonal: usually with rheumatoid factor (RF)
- type III (50%): polyclonal: usually with RF

Type I

- monoclonal - IgG or IgM
- associations: multiple myeloma, Waldenstrom macroglobulinaemia

Type II

- mixed monoclonal and polyclonal: usually with RF
- associations: hepatitis C, RA, Sjogren's, lymphoma

Type III

- polyclonal: usually with RF
- associations: rheumatoid arthritis, Sjogren's

191 fac

Symptoms (if present in high concentrations)

- Raynaud's only seen in type I
- cutaneous: vascular purpura, distal ulceration, ulceration
- arthralgia
- renal involvement (diffuse glomerulonephritis)

Score f

Key fac

Purpur

Smudg

Breast

Tests

- low complement (esp. C4)
- high ESR

Treatment

- immunosuppression
- plasmapheresis

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Question 10

Auer rods

Burkitt

Myelof

Chronic

Acute m

Hodgki

Wiskot

Cyclophosphamide



Cyclophosphamide is an alkylating agent used in the management of cancer and autoimmune conditions. It works by causing cross-linking of DNA

Adverse effects

- haemorrhagic cystitis: incidence reduced by the use of hydration and mesna
- myelosuppression
- transitional cell carcinoma

Mesna

- 2-mercaptoethane sulfonate Na
- a metabolite of cyclophosphamide called acrolein is toxic to urothelium
- mesna binds to and inactivates acrolein helping to prevent haemorrhagic cystitis

B*I*U**A**

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191 fac

Score f

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Key fac

tion

Mesna binds to and inactivates acrolein

[Notes](#)

(1/1)

Purpuric rash, hepatitis C positive - cryoglobulinaemia

[Notes](#)

(1/1)

Smudge/smear cells - chronic lymphocytic leukaemia

[Notes](#)

(0/1)

Breast cancer - risk factors include: early menarche

[Notes](#)

(0/1)

Close

Questions

Abdominal

Lithium

Digoxin

Lead poisoning

Aspirin

191 facts

Score for

3 in a row

Key facts

Auer rods

Mesna

Purpura

Smudged

Breast

Acute myeloid leukaemia

✕

Acute myeloid leukaemia is the more common form of acute leukaemia in adults. It may occur as a primary disease or following a secondary transformation of a myeloproliferative disorder.

Features are largely related to bone marrow failure:

- anaemia: pallor, lethargy
- neutropenia: whilst white cell counts may be very high, functioning neutrophil levels may be low leading to frequent infections etc
- thrombocytopenia: bleeding
- splenomegaly
- bone pain

Poor prognostic features

- > 60 years
- > 20% blasts after first course of chemo
- cytogenetics: deletions of chromosome 5 or 7

Acute promyelocytic leukaemia M3

- associated with t(15;17)
- fusion of PML and RAR-alpha genes
- presents younger than other types of AML (average = 25 years old)
- Auer rods (seen with myeloperoxidase stain)
- DIC or thrombocytopenia often at presentation
- good prognosis

Classification - French-American-British (FAB)

- M0 - undifferentiated
- M1 - without maturation
- M2 - with granulocytic maturation
- M3 - acute promyelocytic
- M4 - granulocytic and monocytic maturation
- M5 - monocytic
- M6 - erythroleukaemia
- M7 - megakaryoblastic

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Lead poisoning

Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of abdominal pain and neurological signs

Features

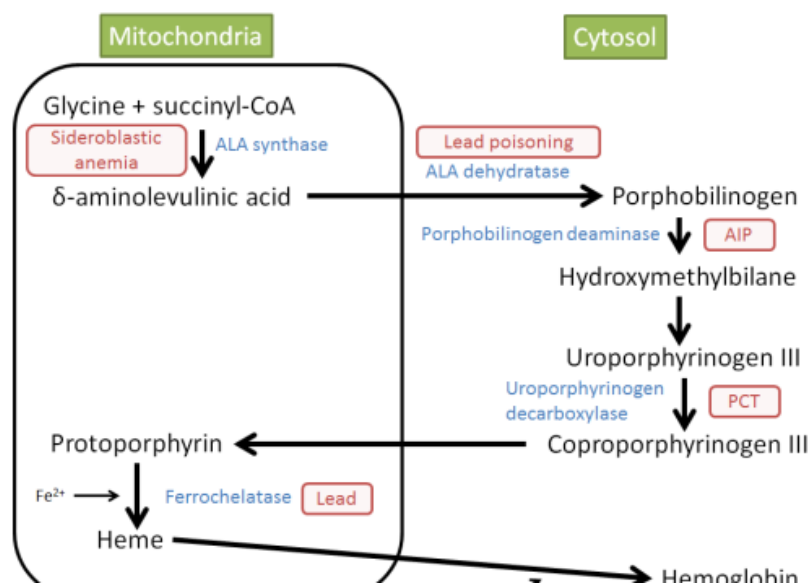
- abdominal pain
- peripheral neuropathy (mainly motor)
- fatigue
- constipation
- blue lines on gum margin (only 20% of adult patients, very rare in children)

Investigations

- the blood lead level is usually used for diagnosis. Levels greater than 10 mcg/dl are considered significant
- full blood count: microcytic anaemia. Blood film shows red cell abnormalities including basophilic stippling and clover-leaf morphology
- raised serum and urine levels of delta aminolaevulinic acid may be seen making it sometimes difficult to differentiate from acute intermittent porphyria
- urinary coproporphyrin is also increased (urinary porphobilinogen and uroporphyrin levels are normal to slightly increased)

Management - various chelating agents are currently used:

- dimercaptosuccinic acid (DMSA)
- D-penicillamine
- EDTA
- dimercaprol





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Bleeding problems, normal platelets, raised bleeding time, slightly raised APTT in a question is most likely to indicate:

Burkitt's lymphoma

Burkitt's lymphoma is a high-grade B-cell neoplasm. There are two major forms:

- endemic (African) form: typically involves maxilla or mandible
- sporadic form: abdominal (e.g. ileo-caecal) tumours are the most common form. More common in patients with HIV

Burkitt's lymphoma is associated with the c-myc gene translocation, usually t(8:14). The Epstein-Barr virus (EBV) is strongly implicated in the development of the African form of Burkitt's lymphoma and to a lesser extent the sporadic form.

Microscopy findings

- 'starry sky' appearance: lymphocyte sheets interspersed with macrophages containing dead apoptotic tumour cells

Management is with chemotherapy. This tends to produce a rapid response which may cause 'tumour lysis syndrome'. Rasburicase (a recombinant version of urate oxidase, an enzyme which catalyses the conversion of uric acid to allantoin*) is often given before the chemotherapy to reduce the risk of this occurring. Complications of tumour lysis syndrome include:

- hyperkalaemia
- hyperphosphataemia
- hypocalcaemia
- hyperuricaemia
- acute renal failure

*allantoin is 5-10 times more soluble than uric acid, so renal excretion is more effective

B**I**U**A**

Tl

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Question

Von Willebrand's disease



Recurrent

Chronic

Paroxysm

Von Willebrand

Wiskott-Rich

Hodgkin's

Monoclonal

191 fac

Score f

3 in a m

Key fac

Bleeding

Lymph

lympho

A 60-v

Von Willebrand's disease is the most common inherited bleeding disorder. The majority of cases are inherited in an autosomal dominant fashion* and characteristically behaves like a platelet disorder i.e. epistaxis and menorrhagia are common whilst haemarthroses and muscle haematomas are rare

Role of von Willebrand factor

- large glycoprotein which forms massive multimers up to 1,000,000 Da in size
- promotes platelet adhesion to damaged endothelium
- carrier molecule for factor VIII

Types

- type 1: partial reduction in vWF (80% of patients)
- type 2: abnormal form of vWF
- type 3: total lack of vWF (autosomal recessive)

Investigation

- prolonged bleeding time
- APTT may be prolonged
- factor VIII levels may be moderately reduced
- defective platelet aggregation with ristocetin

Management

- tranexamic acid for mild bleeding
- desmopressin (DDAVP): raises levels of vWF by inducing release of vWF from Weibel-Palade bodies in endothelial cells
- factor VIII concentrate

*type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

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Reference ranges

End session

Wiskott-Aldrich syndrome



Wiskott-Aldrich syndrome causes primary immunodeficiency due to a combined B- and T-cell dysfunction. It is inherited in a X-linked recessive fashion and is thought to be caused by mutation in the WASP gene.

Features

- recurrent bacterial infections (e.g. Chest)
- eczema
- thrombocytopaenia
- low IgM levels

B*I*U

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Close

191 facts

Score for this session: 73.3%

4 in a row correct

Key facts from this session are shown below (score/attempts), click on the fact for background information

Recurrent bacterial infections, eczema, thrombocytopaenia - Wiskott-Aldrich syndrome

[Notes](#)

(1/1)

Bleeding problems, normal platelets, raised bleeding time, slightly raised APTT - von Willebrand's disease

[Notes](#)

(1/1)

Lymphocyte sheets interspersed with macrophages containing dead apoptotic tumour cells - Burkitt's



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G6PD deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the commonest red blood cell enzyme defect. It is more common in people from the Mediterranean and Africa and is inherited in a X-linked recessive fashion. Many drugs can precipitate a crisis as well as infections and broad (fava) beans

Pathophysiology

- ↓ G6PD → ↓ glutathione → increased red cell susceptibility to oxidative stress

Features

- neonatal jaundice is often seen
- intravascular haemolysis
- gallstones are common
- splenomegaly may be present
- Heinz bodies on blood films

Diagnosis is made by using a G6PD enzyme assay

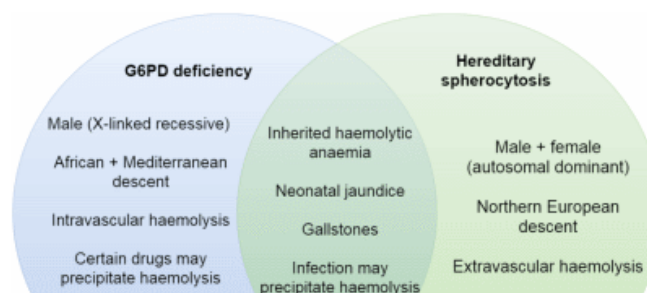
Some drugs causing haemolysis

- anti-malarials: primaquine
- ciprofloxacin
- sulph- group drugs: sulphonamides, sulphasalazine, sulfonyleureas

Some drugs thought to be safe

- penicillins
- cephalosporins
- macrolides
- tetracyclines
- trimethoprim

Comparing G6PD deficiency to hereditary spherocytosis:

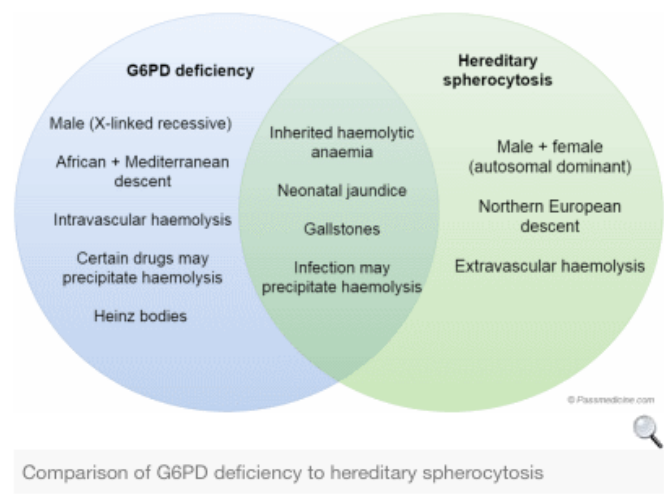


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- penicillins
- cephalosporins
- macrolides
- tetracyclines
- trimethoprim

Comparing G6PD deficiency to hereditary spherocytosis:



	G6PD deficiency	Hereditary spherocytosis
Gender	Male (X-linked recessive)	Male + female (autosomal dominant)
Ethnicity	African + Mediterranean descent	Northern European descent
Typical history	• Neonatal jaundice • Infection/drugs precipitate haemolysis • Gallstones	• Neonatal jaundice • Chronic symptoms although haemolytic crises may be precipitated by infection • Gallstones • Splenomegaly is common
Blood film	Heinz bodies	Spherocytes (round, lack of central pallor)
Diagnostic test	Measure enzyme activity of G6PD	Osmotic fragility test

Question 17

Which one of the following is most likely to result in a **normocytic** anemia?

Lead poisoning

Alcohol

Chronic kidney disease

Congenital sideroblastic anaemia

Liver disease

Iron-deficiency anaemia

Quick comparison: Anaemia classification

Chronic kidney disease

- normocytic

Lead poisoning

- microcytic

Relevant to my revision >

Less relevant >

Normocytic anaemia

Causes of normocytic anaemia include

- anaemia of chronic disease
- chronic kidney disease
- aplastic anaemia
- haemolytic anaemia



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Delicious

Question

Fanconi anaemia



Autosomal recessive

Features

- aplastic anaemia
- increased risk of acute myeloid leukaemia
- neurological
- skeletal abnormalities: short stature
- cafe au lait spots

B*I*U

Save my notes

Close

191 facts

Score for

Key facts from this session are shown below (score/attempts), click on the fact for background information

Aplastic anaemia, cafe au lait spots, short stature, acute myeloid leukaemia - Fanconi anaemia

[Notes](#) (1/1)

Normocytic - chronic kidney disease

[Notes](#) (0/1)

Sulfonylureas may cause haemolysis in patients with G6PD deficiency

[Notes](#) (0/1)

Recurrent bacterial infections, eczema, thrombocytopaenia - Wiskott-Aldrich syndrome

[Notes](#) (0/1)



Cryoglobulinaemia

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Acute myeloid leukaemia

Walden

MGUS



Fancor

Multipl

IgA def

Monoclonal gammopathy of undetermined significance (MGUS, also known as benign paraproteinaemia and monoclonal gammopathy) is a common condition that causes a paraproteinaemia and is often mistaken for myeloma. Differentiating features are listed below. Around 10% of patients eventually develop myeloma at 5 years, with 50% at 15 years

Features

- usually asymptomatic
- no bone pain or increased risk of infections
- around 10-30% of patients have a demyelinating neuropathy

191 fac

Differentiating features from myeloma

- normal immune function
- normal beta-2 microglobulin levels
- lower level of paraproteinaemia than myeloma (e.g. < 30g/l IgG, or < 20g/l IgA)
- stable level of paraproteinaemia
- no clinical features of myeloma (e.g. lytic lesions on x-rays or renal disease)

Score f

Key fac

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Normo

Close

Sulfonylureas may cause haemolysis in patients with G6PD deficiency

Notes

(0/1)

Recurrent bacterial infections, eczema, thrombocytopaenia - Wiskott-Aldrich syndrome

Notes

(1/1)



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Primary immunodeficiency

Primary immunodeficiency disorders may be classified according to which component of the immune system they affect.

Neutrophil disorders

Disorder	Underlying defect	Notes
Chronic granulomatous disease	Lack of NADPH oxidase reduces ability of phagocytes to produce reactive oxygen species	Causes recurrent pneumonias and abscesses, particularly due to catalase-positive bacteria (e.g. <i>Staphylococcus aureus</i>) and fungi (e.g. <i>Aspergillus</i>) Negative nitroblue-tetrazolium test Abnormal dihydrorhodamine flow cytometry test
Chediak-Higashi syndrome	Microtubule polymerization defect which leads to a decrease in phagocytosis	Affected children have 'partial albinism' and peripheral neuropathy. Recurrent bacterial infections are seen Giant granules in neutrophils and platelets
Leukocyte adhesion deficiency	Defect of LFA-1 integrin (CD18) protein on neutrophils	Recurrent bacterial infections. Delay in umbilical cord sloughing may be seen Absence of neutrophils/pus at sites of infection

B-cell disorders

Disorder	Underlying defect	Notes
Common variable immunodeficiency	Many varying causes	Hypogammaglobulinemia is seen. May predispose to autoimmune disorders and lymphoma
Bruton's (x-linked) congenital agammaglobulinaemia	Defect in Bruton's tyrosine kinase (BTK) gene that leads to a severe block in B cell development	X-linked recessive. Recurrent bacterial infections are seen Absence of B-cells with reduced immunoglobulins of all classes
Selective immunoglobulin A deficiency	Maturation defect in B cells	Most common primary antibody deficiency. Recurrent sinus and respiratory infections Associated with coeliac disease and may cause false negative coeliac antibody screen

No SIM 2:48 PM 53%

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deficiency	Absence of neutrophils/pus at sites of infection
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Selective immunoglobulin A deficiency	Maturation defect in B cells	Most common primary antibody deficiency. Recurrent sinus and respiratory infections Associated with coeliac disease and may cause false negative coeliac antibody screen Severe reactions to blood transfusions may occur (anti-IgA antibodies → anaphylaxis)

T-cell disorders

Disorder	Underlying defect	Notes
DiGeorge syndrome	22q11.2 deletion, failure to develop 3rd and 4th pharyngeal pouches	Common features include congenital heart disease (e.g. tetralogy of Fallot), learning difficulties, hypocalcaemia, recurrent viral/fungal diseases, cleft palate

Combined B- and T-cell disorders

Disorder	Underlying defect	Notes
Severe combined immunodeficiency	Many varying causes. Most common (X-linked) due to defect in the common gamma chain, a protein used in the receptors for IL-2 and other	Recurrent infections due to viruses, bacteria and fungi. Reduced T-cell receptor expression similar



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T-cell disorders

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Combined B- and T-cell disorders

Disorder	Underlying defect	Notes
Severe combined immunodeficiency	Many varying causes. Most common (X-linked) due to defect in the common gamma chain, a protein used in the receptors for IL-2 and other interleukins. Other causes include adenosine deaminase deficiency	Recurrent infections due to viruses, bacteria and fungi. Reduced T-cell receptor excision circles Stem cell transplantation may be successful
Ataxia telangiectasia	Defect in DNA repair enzymes	Autosomal recessive. Features include cerebellar ataxia, telangiectasia (spider angiomas), recurrent chest infections and 10% risk of developing malignancy, lymphoma or leukaemia
Wiskott-Aldrich syndrome	Defect in WAS gene	X-linked recessive. Features include recurrent bacterial infections, eczema, thrombocytopaenia. Low IgM levels Increased risk of autoimmune disorders and malignancy



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Hyposplenism Cannot Open Page



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Myeloma: features

Multiple myeloma is a neoplasm of the bone marrow plasma cells. The peak incidence is patients aged 60-70 years.

Clinical features

- bone disease: bone pain, osteoporosis + pathological fractures (typically vertebral), osteolytic lesions
- lethargy
- infection
- hypercalcaemia (see below)
- renal failure
- other features: amyloidosis e.g. Macroglossia, carpal tunnel syndrome; neuropathy; hyperviscosity

Investigations

- monoclonal proteins (usually IgG or IgA) in the serum and urine (Bence Jones proteins)
- increased plasma cells in the bone marrow
- historically a skeletal survey has been done to look for bone lesions. However, whole-body MRI is increasingly used and is now recommended in the 2016 NICE guidelines

The diagnostic criteria for multiple myeloma requires one major and one minor criteria or three minor criteria in an individual who has signs or symptoms of multiple myeloma.

Major criteria

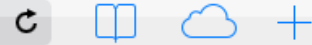
- Plasmacytoma (as demonstrated on evaluation of biopsy specimen)
- 30% plasma cells in a bone marrow sample
- Elevated levels of M protein in the blood or urine

Minor criteria

- 10% to 30% plasma cells in a bone marrow sample.
- Minor elevations in the level of M protein in the blood or urine.
- Osteolytic lesions (as demonstrated on imaging studies).
- Low levels of antibodies (not produced by the cancer cells) in the blood.

Hypercalcaemia in myeloma

- primary factor: due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- much less common contributing factors: impaired renal function, increased renal tubular calcium reabsorption and elevated PTH-rP levels



Question

Myeloma: features

x

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Clinical features

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- lethargy
- infection
- hypercalcaemia (see below)
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Major criteria

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- 30% plasma cells in a bone marrow sample
- Elevated levels of M protein in the blood or urine

Minor criteria

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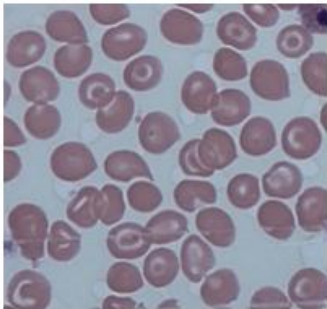
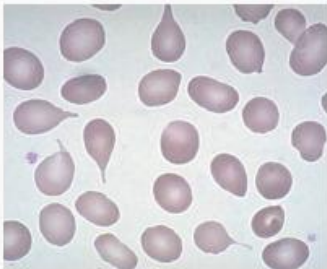
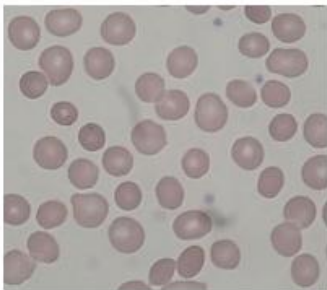
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Blood films: pathological cell forms

Pathological red cell forms

Abnormality	Associated condition(s)	Appearance
Target cells	Sickle-cell/thalassaemia Iron-deficiency anaemia Hyposplenism Liver disease	
'Tear-drop' poikilocytes	Myelofibrosis	
Spherocytes	Hereditary spherocytosis Autoimmune hemolytic anaemia	



sce dermatology books - Google Search

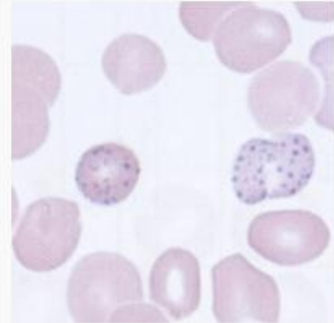


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According To J Season04 Episode 22...

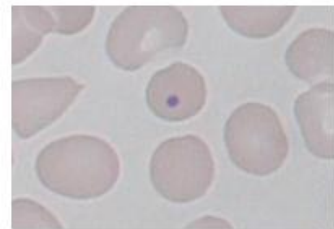
Basophilic stippling

Lead poisoning
Thalassaemia
Sideroblastic anemia
Myelodysplasia



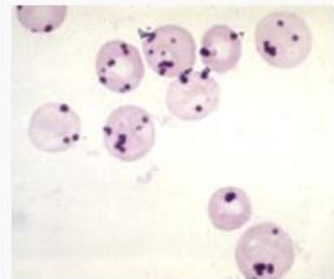
Howell-Jolly bodies

Hyposplenism



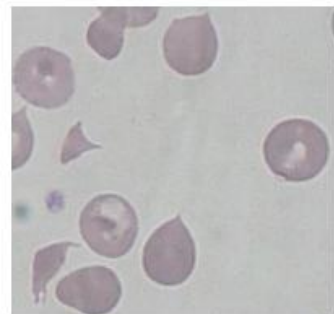
Heinz bodies

G6PD deficiency
Alpha-thalassaemia



Schistocytes ('helmet cells')

Intravascular haemolysis
Mechanical heart valve
Disseminated intravascular coagulation





sce dermatology books - Google Search

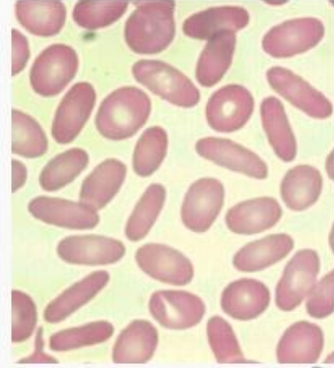


Passmedicine

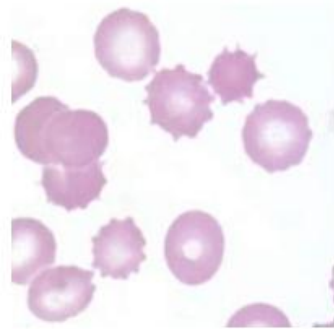
According To J Season04 Episode 22...

'Pencil' poikilocytes

Iron deficiency anaemia

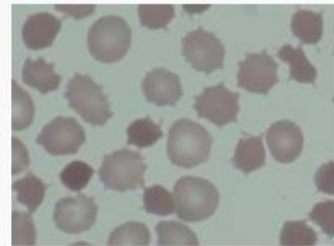


Burr cells (echinocytes)

Uraemia
Pyruvate kinase deficiency

Acanthocytes

Abetalipoproteinemia



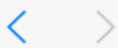
Other blood film abnormalities:

- hypersegmented neutrophils: megaloblastic anaemia

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Palliative care prescribing: pain



NICE guidelines

In 2012 NICE published guidelines on the use of opioids in palliative care. Selected points are listed below. Please see the link for more details.

Starting treatment

- when starting treatment, offer patients with advanced and progressive disease regular oral modified-release (MR) or oral immediate-release morphine (depending on patient preference), with oral immediate-release morphine for breakthrough pain
- if no comorbidities use 20-30mg of MR a day with 5mg morphine for breakthrough pain. For example, 15mg modified-release morphine tablets twice a day with 5mg of oral morphine solution as required
- oral modified-release morphine should be used in preference to transdermal patches
- laxatives should be prescribed for all patients initiating strong opioids
- patients should be advised that nausea is often transient. If it persists then an antiemetic should be offered
- drowsiness is usually transient - if it does not settle then adjustment of the dose should be considered

SIGN guidelines

SIGN issued guidance on the control of pain in adults with cancer in 2008. Selected points

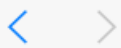
- the breakthrough dose of morphine is one-sixth the daily dose of morphine
- all patients who receive opioids should be prescribed a laxative
- opioids should be used with caution in patients with chronic kidney disease. Alfentanil, buprenorphine and fentanyl are preferred
- metastatic bone pain may respond to strong opioids, bisphosphonates or radiotherapy. The assertion that NSAIDs are particularly effective for metastatic bone pain is not supported by studies. Strong opioids have the lowest number needed to treat for relieving the pain and can provide quick relief, in contrast to radiotherapy and bisphosphonates*. All patients, however, should be considered for referral to a clinical oncologist for consideration of further treatments such as radiotherapy

Other points

When increasing the dose of opioids the next dose should be increased by 30-50%.

Opioid side-effects

[Back to top](#)



Pass

Opioid side-effects

Usually transient	Usually persistent
Nausea Drowsiness	Constipation

Conversion between opioids

From	To	Conversion factor
Oral codeine	Oral morphine	Divide by 10
Oral tramadol	Oral morphine	Divide by 10**

Oxycodone generally causes less sedation, vomiting and pruritis than morphine but more constipation.

From	To	Conversion factor
Oral morphine	Oral oxycodone	Divide by 1.5-2***

The current BNF gives the following conversion factors for transdermal preparations

- a transdermal fentanyl 12 microgram patch equates to approximately 30 mg oral morphine daily
- a transdermal buprenorphine 10 microgram patch equates to approximately 24 mg oral morphine daily.

From	To	Conversion factor
Oral morphine	Subcutaneous morphine	Divide by 2
Oral morphine	Subcutaneous diamorphine	Divide by 3
Oral oxycodone	Subcutaneous diamorphine	Divide by 1.5

*BMJ 2015;350:h315 Cancer induced bone pain

**this has previously been stated as 5 but the current version of the BNF states a

session

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[Back to top](#)

[Less relevant](#)

Chronic myeloid leukaemia

The Philadelphia chromosome is present in more than 95% of patients with chronic myeloid leukaemia (CML). It is due to a translocation between the long arm of chromosome 9 and 22 - t(9:22)(q34; q11). This results in part of the ABL proto-oncogene from chromosome 9 being fused with the BCR gene from chromosome 22. The resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal

Presentation (60-70 years)

- anaemia: lethargy
- weight loss and sweating are common
- splenomegaly may be marked → abdo discomfort
- spectrum of myeloid cells seen in peripheral blood
- decreased leukocyte alkaline phosphatase
- may undergo blast transformation (AML in 80%, ALL in 20%)

Management

- imatinib is now considered first-line treatment
- hydroxyurea
- interferon-alpha
- allogenic bone marrow transplant

Imatinib

- inhibitor of the tyrosine kinase associated with the BCR-ABL defect
- very high response rate in chronic phase CML

[Save my notes](#)

Relevant to my revision

Less relevant

Haemolytic anaemias: by site

In intravascular haemolysis free haemoglobin is released which binds to haptoglobin. As haptoglobin becomes saturated haemoglobin binds to albumin forming methaemalbumin (detected by Schumm's test). Free haemoglobin is excreted in the urine as haemoglobinuria, haemosiderinuria

Intravascular haemolysis: causes

- mismatched blood transfusion
- G6PD deficiency*
- red cell fragmentation: heart valves, TTP, DIC, HUS
- paroxysmal nocturnal haemoglobinuria
- cold autoimmune haemolytic anaemia

Extravascular haemolysis: causes

- haemoglobinopathies: sickle cell, thalassaemia
- hereditary spherocytosis
- haemolytic disease of newborn
- warm autoimmune haemolytic anaemia

*strictly speaking there is an element of extravascular haemolysis in G6PD as well, although it is usually classified as a intravascular cause

B *I* U

Save my notes

Relevant to my revision

Less relevant

Hodgkin's lymphoma

Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterised by the presence of the Reed-Sternberg cell. It has a bimodal age distributions being most common in the third and seventh decades

Features

- lymphadenopathy (75%) - painless, non-tender, asymmetrical
- systemic (25%): weight loss, pruritus, night sweats, fever (Pel-Ebstein)
- alcohol pain in HL
- normocytic anaemia, eosinophilia
- LDH raised



Save my notes

Send feedback

166 facts found

- macrocytic (normoblastic)
- macrocytic (megaloblastic)

Relevant to my revision

Less relevant

Macrocytic anaemia

Macrocytic anaemia can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow

Megaloblastic causes	Normoblastic causes
• vitamin B12 deficiency • folate deficiency	• alcohol • liver disease • hypothyroidism • pregnancy • reticulocytosis • myelodysplasia • drugs: cytotoxics

B *I* U

Save my notes



Pass Cytotoxic agents



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The tables below summarises the mechanism of action and major adverse effects of commonly used cytotoxic agents.

Alkylating agents

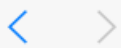
Cytotoxic	Mechanism of action	Adverse effects
Cyclophosphamide	Alkylating agent - causes cross-linking in DNA	Haemorrhagic cystitis, myelosuppression, transitional cell carcinoma

Cytotoxic antibiotics

Cytotoxic	Mechanism of action	Adverse effects
Bleomycin	Degrades preformed DNA	Lung fibrosis
Doxorubicin	Stabilizes DNA-topoisomerase II complex inhibits DNA & RNA synthesis	Cardiomyopathy

Antimetabolites

Cytotoxic	Mechanism of action	Adverse effects
Methotrexate	Inhibits dihydrofolate reductase and thymidylate synthesis	Myelosuppression, mucositis, liver fibrosis, lung fibrosis
Fluorouracil (5-FU)	Pyrimidine analogue inducing cell cycle arrest and apoptosis by blocking thymidylate synthase (works during S phase)	Myelosuppression, mucositis, dermatitis
6-mercaptopurine	Purine analogue that is activated by HGPRTase, decreasing purine synthesis	Myelosuppression
Cytarabine	Pyrimidine antagonist. Interferes with DNA synthesis specifically at the S-phase of the cell cycle and inhibits DNA polymerase	Myelosuppression, ataxia



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Cytotoxic	Mechanism of action	Adverse effects
Methotrexate	Inhibits dihydrofolate reductase and thymidylate synthesis	Myelosuppression, mucositis, liver fibrosis, lung fibrosis
Fluorouracil (5-FU)	Pyrimidine analogue inducing cell cycle arrest and apoptosis by blocking thymidylate synthase (works during S phase)	Myelosuppression, mucositis, dermatitis
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Cytarabine	Pyrimidine antagonist. Interferes with DNA synthesis specifically at the S-phase of the cell cycle and inhibits DNA polymerase	Myelosuppression, ataxia

Acts on microtubules

Cytotoxic	Mechanism of action	Adverse effects
Vincristine, vinblastine	Inhibits formation of microtubules	Vincristine: Peripheral neuropathy (reversible), paralytic ileus Vinblastine: myelosuppression
Docetaxel	Prevents microtubule depolymerisation & disassembly, decreasing free tubulin	Neutropaenia

Other cytotoxic drugs

Cytotoxic	Mechanism of action	Adverse effects
Cisplatin	Causes cross-linking in DNA	Ototoxicity, peripheral neuropathy, hypomagnesaemia
Hydroxyurea (hydroxycarbamide)	Inhibits ribonucleotide reductase, decreasing DNA synthesis	Myelosuppression

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Question 17

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Hereditary spherocytosis

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Basics

- most common hereditary haemolytic anaemia in people of northern European descent
- autosomal dominant defect of red blood cell cytoskeleton
- the normal biconcave disc shape is replaced by a sphere-shaped red blood cell
- red blood cell survival reduced as destroyed by the spleen

Presentation

- failure to thrive
- jaundice, gallstones
- splenomegaly
- aplastic crisis precipitated by parvovirus infection
- degree of haemolysis variable
- MCHC elevated

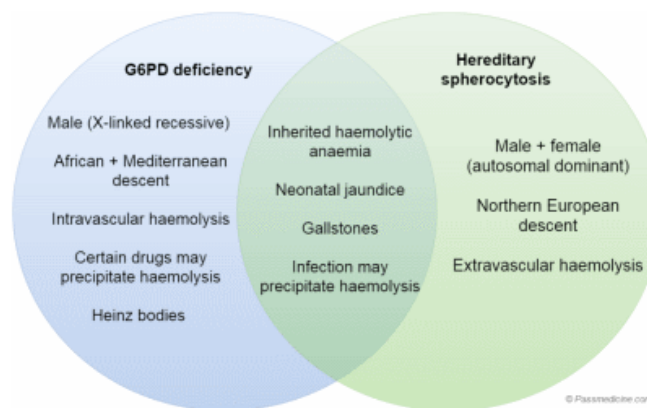
Diagnosis

- osmotic fragility test

Management

- folate replacement
- splenectomy

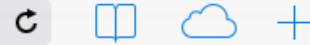
Comparing G6PD deficiency to hereditary spherocytosis:



© Passmedicine.com



Comparison of G6PD deficiency to hereditary spherocytosis



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Polycythaemia vera: features



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Polycythaemia vera (previously called polycythaemia rubra vera) is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an increase in red cell volume, often accompanied by overproduction of neutrophils and platelets. It has recently been established that a mutation in JAK2 is present in approximately 95% of patients with polycythaemia vera and this has resulted in significant changes to the diagnostic criteria. The incidence of polycythaemia vera peaks in the sixth decade.

Features

- hyperviscosity
- pruritus, typically after a hot bath
- splenomegaly
- haemorrhage (secondary to abnormal platelet function)
- plethoric appearance
- hypertension in a third of patients

Following history and examination, the British Committee for Standards in Haematology (BCSH) recommend the following tests are performed

- full blood count/film (raised haematocrit; neutrophils, basophils, platelets raised in half of patients)
- JAK2 mutation
- serum ferritin
- renal and liver function tests

If the JAK2 mutation is negative and there is no obvious secondary causes the BCSH suggest the following tests:

- red cell mass
- arterial oxygen saturation
- abdominal ultrasound
- serum erythropoietin level
- bone marrow aspirate and trephine
- cytogenetic analysis
- erythroid burst-forming unit (BFU-E) culture

Other features that may be seen in PRV include a low ESR and a raised leukocyte alkaline phosphatase

The diagnostic criteria for polycythaemia vera have recently been updated by the BCSH. This replaces the previous polycythaemia vera Study Group criteria.

JAK2-positive polycythaemia vera - diagnosis requires both criteria to be present

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The diagnostic criteria for polycythaemia vera have recently been updated by the BCSH. This replaces the previous polycythaemia vera Study Group criteria.

JAK2-positive polycythaemia vera - diagnosis requires both criteria to be present

Criteria	Notes
A1	High haematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass ($>25\%$ above predicted)
A2	Mutation in JAK2

JAK2-negative PRV - diagnosis requires A1 + A2 + A3 + either another A or two B criteria

Criteria	Notes
A1	Raised red cell mass ($>25\%$ above predicted) OR haematocrit >0.60 in men, >0.56 in women
A2	Absence of mutation in JAK2
A3	No cause of secondary erythrocytosis
A4	Palpable splenomegaly
A5	Presence of an acquired genetic abnormality (excluding BCR-ABL) in the haematopoietic cells
B1	Thrombocytosis (platelet count $>450 \times 10^9/l$)
B2	Neutrophil leucocytosis (neutrophil count $> 10 \times 10^9/l$ in non-smokers; $> 12.5 \times 10^9/l$ in smokers)
B3	Radiological evidence of splenomegaly
B4	Endogenous erythroid colonies or low serum erythropoietin

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Sideroblastic anaemia

Sideroblastic anaemia is a condition where red cells fail to completely form haem, whose biosynthesis takes place partly in the mitochondrion. This leads to deposits of iron in the mitochondria that form a ring around the nucleus called a ring sideroblast. It may be congenital or acquired

Congenital cause: delta-aminolevulinate synthase-2 deficiency

Acquired causes

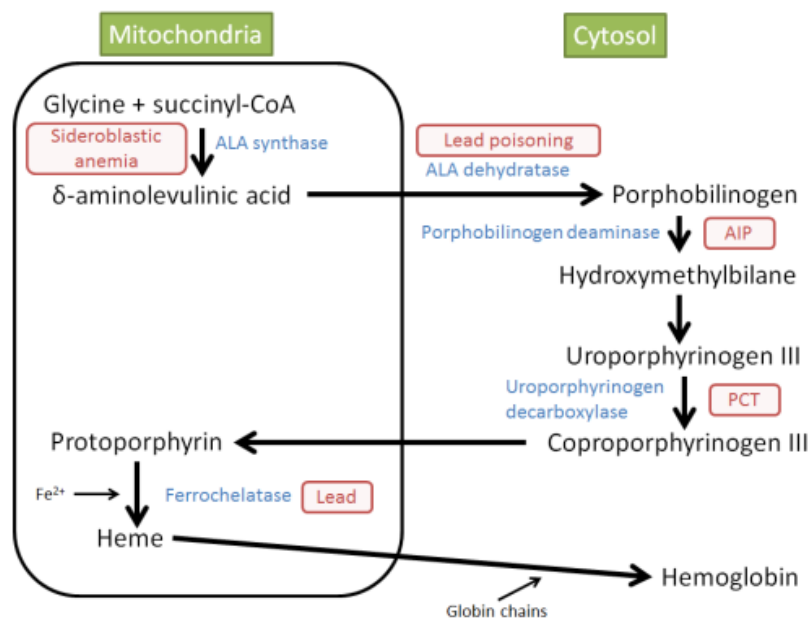
- myelodysplasia
- alcohol
- lead
- anti-TB medications

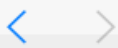
Investigations

- hypochromic microcytic anaemia (more so in congenital)
- bone marrow: sideroblasts and increased iron stores

Management

- supportive
- treat any underlying cause
- pyridoxine may help





Question

Hereditary angioedema



Massive s

Sjogren

SLE

Fanconi

Cystin

Wilson

Myelof

Hereditary angioedema is an autosomal dominant condition associated with low plasma levels of the C1 inhibitor (C1-INH) protein. C1-INH is a multifunctional serine protease inhibitor - the probable mechanism behind attacks is uncontrolled release of bradykinin resulting in oedema of tissues.

Investigation

- C1-INH level is low during an attack
- low C2 and C4 levels are seen, even between attacks. Serum C4 is the most reliable and widely used screening tool

Symptoms

- attacks may be preceded by painful macular rash
- painless, non-pruritic swelling of subcutaneous/submucosal tissues
- may affect upper airways, skin or abdominal organs (can occasionally present as abdominal pain due to visceral oedema)
- urticaria is not usually a feature

Management

- acute: IV C1-inhibitor concentrate, fresh frozen plasma (FFP) if this is not available
- prophylaxis: anabolic steroid Danazol may help

B*I*U**A**

Save my notes

Patient.info

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[Hereditary angioedema review](#)

Fluorou



Myelofibrosis

- massive splenomegaly

Wilson's diseases

- type 2 renal tubular acidosis

Relevant to my revision

Less relevant

Splenomegaly

Massive splenomegaly

- myelofibrosis
- chronic myeloid leukaemia
- visceral leishmaniasis (kala-azar)
- malaria
- Gaucher's syndrome

Other causes (as above plus)

- portal hypertension e.g. secondary to cirrhosis
- lymphoproliferative disease e.g. CLL, Hodgkin's
- haemolytic anaemia
- infection: hepatitis, glandular fever
- infective endocarditis
- sickle-cell*, thalassaemia
- rheumatoid arthritis (Felty's syndrome)

*the majority of adults patients with sickle-cell will have an atrophied spleen due to repeated infarction

B *I* U

Save my notes

Less relevant

Thrombocytosis

Thrombocytosis is an abnormally high platelet count, usually $> 400 \times 10^9/l$.

Causes of thrombocytosis

- reactive: platelets are an acute phase reactant - platelet count can increase in response to stress such as a severe infection or surgery
- malignancy
- essential thrombocytosis (see below), or as part of another myeloproliferative disorder such as chronic myeloid leukaemia or polycythaemia rubra vera
- hyposplenism

Essential thrombocytosis

Essential thrombocytosis is one of the myeloproliferative disorders which overlaps with chronic myeloid leukaemia, polycythaemia rubra vera and myelofibrosis. Megakaryocyte proliferation results in an overproduction of platelets.

Features

- platelet count $> 600 \times 10^9/l$
- both thrombosis (venous or arterial) and haemorrhage can be seen
- a characteristic symptom is a burning sensation in the hands
- a JAK2 mutation is found in around 50% of patients

Management

- hydroxyurea (hydroxycarbamide) is widely used to reduce the platelet count
- interferon- α is also used in younger patients
- low-dose aspirin may be used to reduce the thrombotic risk

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Acute intermittent porphyria

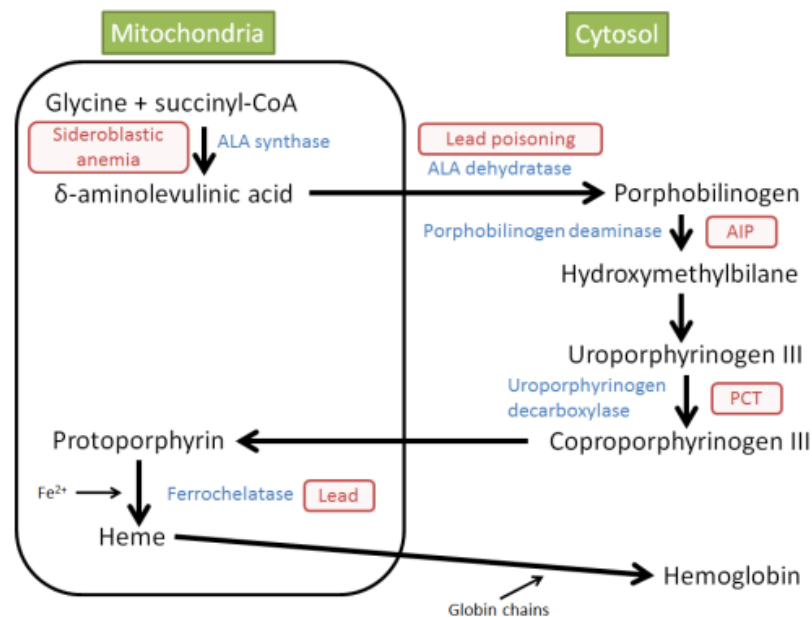
Acute intermittent porphyria (AIP) is a rare autosomal dominant condition caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem. The results in the toxic accumulation of delta aminolaevulinic acid and porphobilinogen. It characteristically presents with abdominal and neuropsychiatric symptoms in 20-40 year olds. AIP is more common in females (5:1)

Features

- abdominal: abdominal pain, vomiting
- neurological: motor neuropathy
- psychiatric: e.g. depression
- hypertension and tachycardia common

Diagnosis

- classically urine turns deep red on standing
- raised urinary porphobilinogen (elevated between attacks and to a greater extent during acute attacks)
- assay of red cells for porphobilinogen deaminase
- raised serum levels of delta aminolaevulinic acid and porphobilinogen



B cell lymphoma of MALT tissue

Gastric carcinoma

Quick comparison: Carcinogens

Hepatocellular carcinoma

- aflatoxin

Squamous cell carcinoma of the bladder cancer

- schistosomiasis

Relevant to my revision

Less relevant

Carcinogens

Carcinogen	Cancer
Aflatoxin (produced by <i>Aspergillus</i>)	Liver - (hepatocellular carcinoma)
Aniline dyes	Bladder (transitional cell carcinoma)
Asbestos	Mesothelioma and bronchial carcinoma
Nitrosamines	Oesophageal and gastric cancer
Vinyl chloride	Hepatic angiosarcoma

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Question 16

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Score for this session: 60%

5 in a row correct

Key facts from this session are shown below (score/attempts), click on the fact for background information

Normocytic - aplastic anaemia

[Notes](#) (1/1)

Doxorubicin may cause cardiomyopathy

[Notes](#) (1/1)

Docetaxel - prevents microtubule depolymerisation & disassembly, decreasing free tubulin

[Notes](#) (1/1)

Target cells - liver disease

[Notes](#) (1/1)

Normocytic anaemia



Causes of normocytic anaemia include

- anaemia of chronic disease
- chronic kidney disease
- aplastic anaemia
- haemolytic anaemia

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Close



Haemophilia



Haemophilia is a X-linked recessive disorder of coagulation. Up to 30% of patients have no family history of the condition. Haemophilia A is due to a deficiency of factor VIII whilst in haemophilia B (Christmas disease) there is a lack of factor IX

Features

- haemarthroses, haematomas
- prolonged bleeding after surgery or trauma

Blood tests

- prolonged APTT
- bleeding time, thrombin time, prothrombin time normal

Up to 10-15% of patients with haemophilia A develop antibodies to factor VIII treatment

B *I* U

Save my notes



[Haemophilia - causes, symptoms, diagnosis, treatment, pathology](#)

Osmosis - YouTube

↑ 17 ↓ 1



Microcytic anaemia



Causes

- iron-deficiency anaemia
- thalassaemia*
- congenital sideroblastic anaemia
- anaemia of chronic disease (more commonly a normocytic, normochromic picture)
- lead poisoning

*in beta-thalassaemia minor the microcytosis is often disproportionate to the anaemia

A question sometimes seen in exams gives a history of a normal haemoglobin level associated with a microcytosis. In patients not at risk of thalassaemia, this should raise the possibility of polycythaemia rubra vera which may cause an iron-deficiency secondary to bleeding.

B*I*U**A**

Save my notes

Close

Microcytic - iron-deficiency anaemia

[Notes](#) (1/1)

Haemophilia A - deficiency of factor VIII

[Notes](#) (1/1)

Normocytic - aplastic anaemia

[Notes](#) (1/1)



Severe combined immunodeficiency

DiGeorge

Common

Ataxic

ITP



Idiopathic thrombocytopenic purpura (ITP) is an immune mediated reduction in the platelet count. Antibodies are directed against the glycoprotein IIb/IIIa or Ib-V-IX complex.

ITP can be divided into acute and chronic forms:

Acute ITP

- more commonly seen in children
- equal sex incidence
- may follow an infection or vaccination
- usually runs a self-limiting course over 1-2 weeks

Chronic ITP

- more common in young/middle-aged women
- tends to run a relapsing-remitting course

Evan's syndrome

- ITP in association with autoimmune haemolytic anaemia (AIHA)

B*I*U**A****T!**Save my notes

British Committee for Standards in Haematology

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[2003 ITP guidelines](#)

Close

Haemophilia A - deficiency of factor VIII

Notes (1/1)

- chronic myeloid leukaemia
- acute promyelocytic leukaemia (M3)

Relevant to my revision

Less relevant

Chronic myeloid leukaemia

The Philadelphia chromosome is present in more than 95% of patients with chronic myeloid leukaemia (CML). It is due to a translocation between the long arm of chromosome 9 and 22 - t(9:22)(q34; q11). This results in part of the ABL proto-oncogene from chromosome 9 being fused with the BCR gene from chromosome 22. The resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal

Presentation (60-70 years)

- anaemia: lethargy
- weight loss and sweating are common
- splenomegaly may be marked → abdo discomfort
- spectrum of myeloid cells seen in peripheral blood
- decreased leukocyte alkaline phosphatase
- may undergo blast transformation (AML in 80%, ALL in 20%)

Management

- imatinib is now considered first-line treatment
- hydroxyurea
- interferon-alpha
- allogenic bone marrow transplant

Imatinib

- inhibitor of the tyrosine kinase associated with the BCR-ABL defect
- very high response rate in chronic phase CML

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Save my notes



Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is caused by a monoclonal proliferation of well-differentiated lymphocytes which are almost always B-cells (99%)

Features

- often none
- constitutional: anorexia, weight loss
- bleeding, infections
- lymphadenopathy more marked than CML

Complications

- hypogammaglobulinaemia leading to recurrent infections
- warm autoimmune haemolytic anaemia in 10-15% of patients
- transformation to high-grade lymphoma (Richter's transformation)

Investigations

- blood film: smudge cells (also known as smear cells)
- immunophenotyping

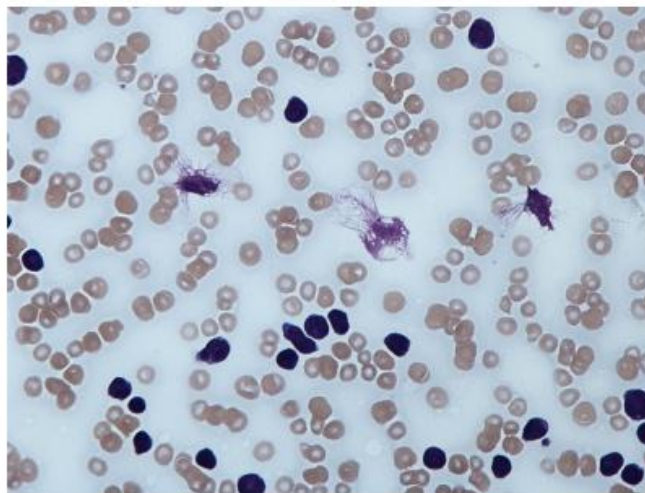


Image sourced from Wikipedia

Peripheral blood film showing smudge B cells

B*I*U**S****A****T!**



Question

Mantle cell lymphoma



Overview

- type of B-cell lymphoma

Genetics

- CD5+, CD19+, CD22+, CD23-, CD10-
- associated translocation (11;14) causing over-expression of the cyclin D1 (BCL-1) gene

Features

- widespread lymphadenopathy
- poor prognosis

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Save my notes

Close

Mantle cell lymphoma - over-expression of cyclin D1

[Notes](#)

(1/1)

Normocytic - haemolytic anaemia

[Notes](#)

(1/1)

Massive splenomegaly may be caused by visceral leishmaniasis

[Notes](#)

(1/1)

Each one of the following is associated with polycythaemia vera, except:

Splenomegaly	13%
Hyperviscosity	4%
Raised ESR	48%
Hypertension	25%
Pruritus	9%

Polycythaemia rubra vera is associated with a low ESR



Next question >

Polycythaemia vera: features

Polycythaemia vera (previously called polycythaemia rubra vera) is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an increase in red cell volume, often accompanied by overproduction of neutrophils and platelets. It has recently been established that a mutation in JAK2 is present in approximately 95% of patients with polycythaemia vera and this has resulted in significant changes to the diagnostic criteria. The incidence of polycythaemia vera peaks in the sixth decade.

Features

- hyperviscosity
- pruritus, typically after a hot bath
- splenomegaly
- haemorrhage (secondary to abnormal platelet function)
- plethoric appearance

Deep vein thrombosis: diagnosis and management

Diagnosis

NICE published guidelines in 2012 relating to the investigation and management of deep vein thrombosis (DVT).

If a patient is suspected of having a DVT a two-level DVT Wells score should be performed:

Two-level DVT Wells score

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	-2

Deep vein thrombosis: diagnosis and management

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Clinical probability simplified score

- DVT likely: 2 points or more
- DVT unlikely: 1 point or less

If a DVT is 'likely' (2 points or more)

- a proximal leg vein ultrasound scan should be carried out within 4 hours and, if the result is negative, a D-dimer test
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours a D-dimer test should be performed and low-molecular weight heparin administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

If a DVT is 'unlikely' (1 point or less)

- perform a D-dimer test and if it is positive arrange:
- a proximal leg vein ultrasound scan within 4 hours
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours low-molecular weight heparin should be administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

Management

Low molecular weight heparin (LMWH) or fondaparinux should be given initially after a DVT is diagnosed.

- a vitamin K antagonist (i.e. warfarin) should be given within 24 hours of the diagnosis
- the LMWH or fondaparinux should be continued for at least 5 days or until the international normalised ratio (INR) is 2.0 or above for at least 24 hours, whichever is longer, i.e. LMWH or fondaparinux is given at the same time as warfarin until the INR is in the therapeutic range
- warfarin should be continued for at least 3 months. At 3 months, NICE advise that clinicians should 'assess the risks and benefits of extending treatment'
- NICE add 'consider extending warfarin beyond 3 months for patients with *unprovoked* proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding'. This essentially means that if there was no obvious cause or provoking factor (surgery, trauma, significant immobility) it may imply the patient has a tendency to thrombosis and should be given treatment longer than the norm of 3 months. In practice most clinicians give 6 months of warfarin for patients with an unprovoked DVT/PE
- for patients with active cancer NICE recommend using LMWH for 6 months



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Further investigations and thrombophilia screening

As both malignancy and thrombophilia are obvious risk factors for deep vein thrombosis NICE make recommendations on how to investigate patients with unprovoked clots.

Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:

- a physical examination (guided by the patient's full history) and
- a chest X-ray and
- blood tests (full blood count, serum calcium and liver function tests) and urinalysis.

Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE

Thrombophilia screening

- not offered if patients will be on lifelong warfarin (i.e. won't alter management)
- consider testing for antiphospholipid antibodies if unprovoked DVT or PE
- consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE

Each one of the following is seen in Wiskott-Aldrich syndrome, except:

Thrombocytopenia	10%
Recurrent chest infections	6%
X-linked recessive inheritance	14%
Mutation in the WASP gene	7%
Psoriasis	63%

  [Discuss](#) [Improve](#)

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Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome causes primary immunodeficiency due to a combined B- and T-cell dysfunction. It is inherited in a X-linked recessive fashion and is thought to be caused by mutation in the WASP gene.

Features

- recurrent bacterial infections (e.g. Chest)
- eczema
- thrombocytopaenia
- low IgM levels

[Next question >](#)

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Next question >

Cancer in the UK

The most common causes of cancer in the UK are as follows*

- 1. Breast
- 2. Lung
- 3. Colorectal
- 4. Prostate
- 5. Bladder
- 6. Non-Hodgkin's lymphoma
- 7. Melanoma
- 8. Stomach
- 9. Oesophagus
- 10. Pancreas

The most common causes of death from cancer in the UK are as follows:

- 1. Lung
- 2. Colorectal
- 3. Breast
- 4. Prostate
- 5. Pancreas
- 6. Oesophagus
- 7. Stomach
- 8. Bladder
- 9. Non-Hodgkin's lymphoma
- 10. Ovarian

*excludes non-melanoma skin cancer

Next question >



Haematological malignancies: infections



Viruses

- EBV: Hodgkin's and Burkitt's lymphoma, nasopharyngeal carcinoma
- HTLV-1: Adult T-cell leukaemia/lymphoma
- HIV-1: High-grade B-cell lymphoma

Bacteria

- *Helicobacter pylori*: gastric lymphoma (MALT)

Protozoa

- malaria: Burkitt's lymphoma



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Close

HTLV-1 may cause adult T-cell leukaemia/lymphoma

[Notes](#)

(1/1)



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Reference ranges

End session

Tumour lysis syndrome



Tumour lysis syndrome (TLS) is a potentially deadly condition related to the treatment of high grade lymphomas and leukaemias. It can occur in the absence of chemotherapy but is usually triggered by the introduction of combination chemotherapy. On occasion it can occur with steroid treatment alone. Awareness of the condition is critical as prophylactic medication can be given to prevent the potentially deadly effects of tumour cell lysis.

Patients at high risk of TLS should be given IV allopurinol or IV rasburicase immediately prior to and during the first days of chemotherapy. Rasburicase is a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin. Allantoin is much more water soluble than uric acid and is therefore more easily excreted by the kidneys. Patients in lower risk groups should be given oral allopurinol during chemotherapy cycles in an attempt to avoid the condition.

TLS occurs from the breakdown of the tumour cells and the subsequent release of chemicals from the cell. It leads to a high potassium and high phosphate level in the presence of a low calcium. It should be suspected in any patient presenting with an acute kidney injury in the presence of a high phosphate and high uric acid level.

From 2004 TLS has been graded using the Cairo-Bishop scoring system -
Laboratory tumor lysis syndrome: abnormality in two or more of the following, occurring within three days before or seven days after chemotherapy.

- uric acid > 475umol/l or 25% increase
- potassium > 6 mmol/l or 25% increase
- phosphate > 1.125mmol/l or 25% increase
- calcium < 1.75mmol/l or 25% decrease

Clinical tumor lysis syndrome: laboratory tumor lysis syndrome plus one or more of the following:

- increased serum creatinine (1.5 times upper limit of normal)
- cardiac arrhythmia or sudden death
- seizure

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Quick comparison: Features (haematological malignancy)

Deletion of the long arm of chromosome 13

- chronic lymphocytic leukaemia

BCR-ABL fusion protein

- chronic myeloid leukaemia

 Relevant to my revision >

 Less relevant >

Chronic lymphocytic leukaemia: prognostic factors

Poor prognostic factors (median survival 3-5 years)

- male sex
- age > 70 years
- lymphocyte count > 50
- prolymphocytes comprising more than 10% of blood lymphocytes
- lymphocyte doubling time < 12 months
- raised LDH
- CD38 expression positive

Chromosomal changes

- deletion of the long arm of chromosome 13 (del 13q) is the most common abnormality, being seen in around 50% of patients. It is associated with a good prognosis
- deletions of part of the short arm of chromosome 17 (del 17p) are seen in around 5-10% of patients and are associated with a poor prognosis

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Tumour markers

Tumour markers may be divided into:

- monoclonal antibodies against carbohydrate or glycoprotein tumour antigens
- tumour antigens
- enzymes (alkaline phosphatase, neurone specific enolase)
- hormones (e.g. calcitonin, ADH)

It should be noted that tumour markers usually have a low specificity

Monoclonal antibodies

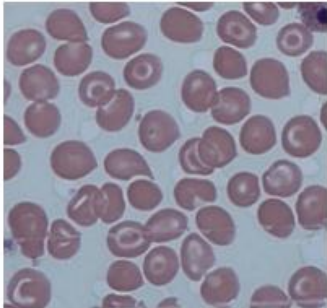
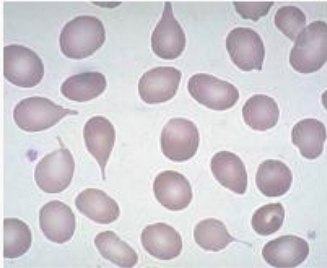
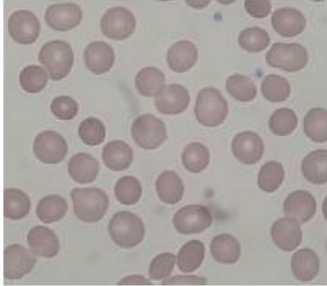
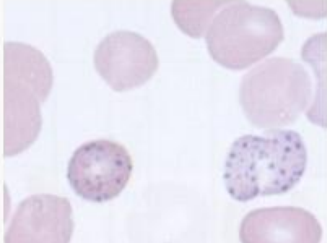
Tumour marker	Association
CA 125	Ovarian cancer
CA 19-9	Pancreatic cancer
CA 15-3	Breast cancer

Tumour antigens

Tumour marker	Association
Prostate specific antigen (PSA)	Prostatic carcinoma
Alpha-feto protein (AFP)	Hepatocellular carcinoma, teratoma
Carcinoembryonic antigen (CEA)	Colorectal cancer
S-100	Melanoma, schwannomas
Bombesin	Small cell lung carcinoma, gastric cancer, neuroblastoma

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Abnormality	Associated condition(s)	Appearance
Target cells	Sickle-cell/thalassaemia Iron-deficiency anaemia Hyposplenism Liver disease	
'Tear-drop' poikilocytes	Myelofibrosis	
Spherocytes	Hereditary spherocytosis Autoimmune hemolytic anaemia	
Basophilic stippling	Lead poisoning Thalassaemia Sideroblastic anemia Myelodysplasia	



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Reference ranges

End session

Normocytic anaemia



Causes of normocytic anaemia include

- anaemia of chronic disease
- chronic kidney disease
- aplastic anaemia
- haemolytic anaemia

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Close

82 facts found

Score for this session: **64.7%**

2 in a row correct

Key facts from this session are shown below (score/attempts), click on the fact for background information

Normocytic - anaemia of chronic disease

[Notes](#)

(1/1)

Hodgkin's lymphoma (nodular sclerosing) - has a good prognosis and is most common

[Notes](#)

(1/1)

Macrocytic (normoblastic) - liver disease

[Notes](#)

(0/1)

T(8:14)

T(15:17)

Quick comparison: Features (haematological malignancy)

T(11:14)

- mantle cell lymphoma

T(14:18)

- follicular lymphoma

Relevant to my revision

Less relevant

Mantle cell lymphoma

Overview

- type of B-cell lymphoma

Genetics

- CD5+, CD19+, CD22+, CD23-, CD10-
- associated translocation (11;14) causing over-expression of the cyclin D1 (BCL-1) gene

Features

- widespread lymphadenopathy
- poor prognosis

B I U

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🔼 Less relevant ➤

Factor V Leiden

Factor V Leiden (activated protein C resistance) is the most common inherited thrombophilia, being present in around 5% of the UK population.

It is due to a gain of function mutation in the Factor V Leiden protein. The result of the mis-sense mutation is that activated factor V (a clotting factor) is inactivated 10 times more slowly by activated protein C than normal. This explains the alternative name for factor V Leiden of activated protein C resistance,

Heterozygotes have a 4-5 fold risk of venous thrombosis. Homozygotes have a 10 fold risk of venous thrombosis but the prevalence is much lower at 0.05%.

Screening for factor V Leiden is not recommended, even after a venous thromboembolism. The logic behind this is that a previous thromboembolism itself is a risk factor for further events and this should dictate specific management in the future, rather than the particular thrombophilia identified.

The table below shows the prevalence and relative risk of venous thromboembolism (VTE) of the different inherited thrombophilias:

Condition	Prevalence	Relative risk of VTE
Factor V Leiden (heterozygous)	5%	4
Factor V Leiden (homozygous)	0.05%	10
Prothrombin gene mutation (heterozygous)	1.5%	3
Protein C deficiency	0.3%	10
Protein S deficiency	0.1%	5-10
Antithrombin III deficiency	0.02	10-20

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Lung cancer: non-small cell

There are three main subtypes of non-small cell lung cancer:

Squamous cell cancer

- typically central
- associated with parathyroid hormone-related protein (PTHrP) secretion → hypercalcaemia
- strongly associated with finger clubbing
- hypertrophic pulmonary osteoarthropathy (HPOA)

Adenocarcinoma

- typically peripheral
- most common type of lung cancer in non-smokers, although the majority of patients who develop lung adenocarcinoma are smokers

Large cell lung carcinoma

- typically peripheral
- anaplastic, poorly differentiated tumours with a poor prognosis
- may secrete β -hCG

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Radiopaedia

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[Lung cancer review](#)

Squamous cell carcinoma

Adenocarcinoma

Large-cell undifferentiated carcinoma

Small-cell carcinoma

Squamous cell carcinoma

- Smokers (98%)
- Often arises centrally/proximally in larger bronchi more than peripheral lung
 - Occurs in bronchi more than larynx and trachea bc flow more turbulent
- Associated with hypercalcaemia (secretes PTH-like compd); causing weakness, dehydration, AMS
- Might see desmosomes and/or keratin accumulation (keratin pearls)
- Can cause obstruction of airway, atelectasis, collapse of lung

Question 54

What is the treatment of choice for **chronic lymphocytic leukaemia (requiring treatment)**?

Frovatriptan or zolmitriptan

Citalopram

Fludarabine, cyclophosphamide and rituximab (FCR)

Doxycycline

Imatinib

Primaquine

Quick comparison: Treatment of choice

Fludarabine, cyclophosphamide and rituximab (FCR)
• chronic lymphocytic leukaemia (requiring treatment)

Imatinib
• chronic myeloid leukaemia

👍 Relevant to my revision >

👎 Less relevant >

Chronic lymphocytic leukaemia: management

Indications for treatment

- progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia
- massive (>10 cm) or progressive lymphadenopathy
- massive (>6 cm) or progressive splenomegaly
- progressive lymphocytosis: > 50% increase over 2 months or lymphocyte doubling time < 6 months
- systemic symptoms: weight loss > 10% in previous 6 months, fever >38°C for > 2 weeks, extreme fatigue, night sweats
- autoimmune cytopenias e.g. ITP

Quick comparison: Treatment of choice

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Imatinib

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👍 Relevant to my revision ➤

 Less relevant

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- autoimmune cytopaenias e.g. ITP

Management

- patients who have no indications for treatment are monitored with regular blood counts
- fludarabine, cyclophosphamide and rituximab (FCR) has now emerged as the initial treatment of choice for the majority of patients

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Blood films: typical pictures



Hyposplenism e.g. post-splenectomy

- target cells
- Howell-Jolly bodies
- Pappenheimer bodies
- siderotic granules
- acanthocytes

Iron-deficiency anaemia

- target cells
- 'pencil' poikilocytes
- if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells

Myelofibrosis

- 'tear-drop' poikilocytes

Intravascular haemolysis

- schistocytes

Megaloblastic anaemia

- hypersegmented neutrophils

B *I* U

Save my notes

Close

Burkitt's lymphoma (treated with chemotherapy) is most associated with which one of the following complications:

- Cryoglobulinaemia
- Osteomalacia
- Warm autoimmune haemolytic anaemia
- Transformation to high-grade lymphoma
- Tumour lysis syndrome**

Subfertility

Quick comparison: Complications

Tumour lysis syndrome

- Burkitt's lymphoma (treated with chemotherapy)

Subfertility

- coeliac disease

Relevant to my revision

Less relevant

Burkitt's lymphoma

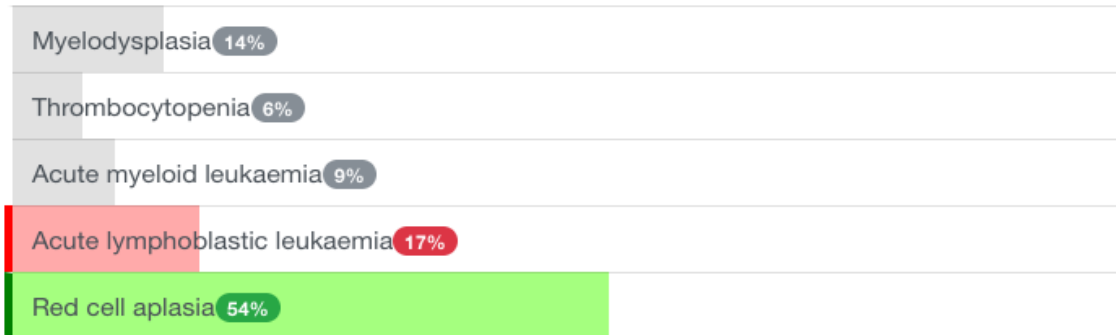
Burkitt's lymphoma is a high-grade B-cell neoplasm. There are two major forms:

- endemic (African) form: typically involves maxilla or mandible
- sporadic form: abdominal (e.g. ileo-caecal) tumours are the most common form. More common in patients with HIV

Burkitt's lymphoma is associated with the c-myc gene translocation, usually t(8:14). The Epstein-Barr virus (EBV) is strongly implicated in the development of the African form of Burkitt's lymphoma and to a lesser extent the sporadic form.

Microscopy findings

Which of the following is most associated with thymomas?



Next question >

Thymoma

Thymomas are the most common tumour of the anterior mediastinum and is usually detected between the sixth and seventh decades of life.

Associated with

- myasthenia gravis (30-40% of patients with thymoma)
- red cell aplasia
- dermatomyositis
- also : SLE, SIADH

Causes of death

- compression of airway
- cardiac tamponade



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Superior vena cava obstruction

Superior vena cava (SVC) obstruction is an oncological emergency caused by compression of the SVC. It is most commonly associated with lung cancer.

Features

- dyspnoea is the most common symptom
- swelling of the face, neck and arms - conjunctival and periorbital oedema may be seen
- headache
- visual disturbance
- pulseless jugular venous distension

Causes

- common malignancies: small cell lung cancer, lymphoma
- other malignancies: metastatic seminoma, Kaposi's sarcoma, breast cancer
- aortic aneurysm
- mediastinal fibrosis
- goitre
- SVC thrombosis

Management

- general: dexamethasone, balloon venoplasty, stenting
- small cell: chemotherapy + radiotherapy
- non-small cell: radiotherapy

Next question >

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Next question >

Eosinophilia

Causes of eosinophilia may be divided into pulmonary, infective and other

Pulmonary causes

- asthma
- allergic bronchopulmonary aspergillosis
- Churg-Strauss syndrome
- Löffler's syndrome
- tropical pulmonary eosinophilia
- eosinophilic pneumonia
- hypereosinophilic syndrome

Infective causes

- schistosomiasis
- nematodes: Toxocara, Ascaris, Strongyloides
- cestodes: Echinococcus

Other causes

- drugs: sulfasalazine, nitrofurantoin
- psoriasis/eczema
- eosinophilic leukaemia (very rare)

Next question >

B I

Which one of the following statements regarding the aetiology of venous thromboembolism (VTE) is correct?

Third generation combined oral contraceptive pills are safer than second generation ones	16%
VTE develops in around 5% of patients with Goodpasture's syndrome	6%
Female gender is a risk factor recurrent VTE	14%
The second trimester of pregnancy is associated with a greater risk than the puerperium	7%
Tamoxifen therapy increases the risk of VTE	57%

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Venous thromboembolism: risk factors

Common predisposing factors include malignancy, pregnancy and the period following an operation. The comprehensive list below is partly based on the 2010 SIGN venous thromboembolism (VTE) guidelines:

General

- increased risk with advancing age
- obesity
- family history of VTE
- pregnancy (especially puerperium)
- immobility
- hospitalisation
- anaesthesia
- central venous catheter: femoral >> subclavian

No SIM 5:54 PM 34%

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Discuss (1) Improve

Next question >

Haematological malignancies: genetics

Below is a brief summary of the common translocations associated with haematological malignancies

t(9;22) - Philadelphia chromosome

- present in > 95% of patients with CML
- this results in part of the Abelson proto-oncogene being moved to the BCR gene on chromosome 22
- the resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal
- poor prognostic indicator in ALL

t(15;17)

- seen in acute promyelocytic leukaemia (M3)
- fusion of PML and RAR-alpha genes

t(8;14)

- seen in Burkitt's lymphoma
- MYC oncogene is translocated to an immunoglobulin gene

t(11;14)

- Mantle cell lymphoma
- deregulation of the cyclin D1 (BCL-1) gene

Next question >

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Next question >

Thrombocytosis

Thrombocytosis is an abnormally high platelet count, usually $> 400 \times 10^9/l$.

Causes of thrombocytosis

- reactive: platelets are an acute phase reactant - platelet count can increase in response to stress such as a severe infection or surgery
- malignancy
- essential thrombocytosis (see below), or as part of another myeloproliferative disorder such as chronic myeloid leukaemia or polycythaemia rubra vera
- hyposplenism

Essential thrombocytosis

Essential thrombocytosis is one of the myeloproliferative disorders which overlaps with chronic myeloid leukaemia, polycythaemia rubra vera and myelofibrosis. Megakaryocyte proliferation results in an overproduction of platelets.

Features

- platelet count $> 600 \times 10^9/l$
- both thrombosis (venous or arterial) and haemorrhage can be seen
- a characteristic symptom is a burning sensation in the hands
- a JAK2 mutation is found in around 50% of patients

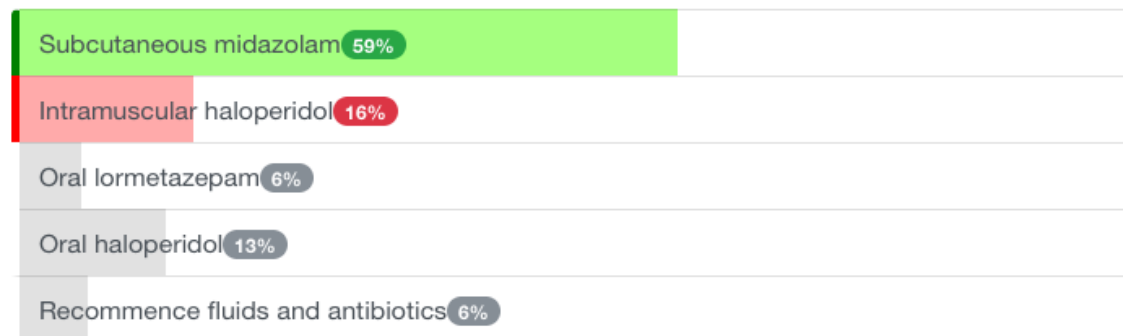
Management

- hydroxyurea (hydroxycarbamide) is widely used to reduce the platelet count
- interferon- α is also used in younger patients
- low-dose aspirin may be used to reduce the thrombotic risk

Next question >

B I

A 79-year-old female with a history of COPD and metastatic lung cancer is admitted with increasing shortness of breath. Following discussion with family it is decided to withdraw active treatment, including fluids and antibiotics, as the admission likely represents a terminal event. Two days after admission she becomes agitated and restless. What is the most appropriate management?



  Discuss (3) Improve

Next question >

Palliative care prescribing: agitation and confusion

Underlying causes of confusion need to be looked for and treated as appropriate, for example hypercalcaemia, infection, urinary retention and medication. If specific treatments fail then the following may be tried:

- first choice: haloperidol
- other options: chlorpromazine, levomepromazine

In the terminal phase of the illness then agitation or restlessness is best treated with midazolam

Next question >

B I

Hypercalcaemia 5%

Paraneoplastic peripheral neuropathy 11%

The upper motor neuron signs point towards a diagnosis of spinal cord compression above L1, rather than cauda equina syndrome.



Next question >

Spinal cord compression

Spinal cord compression is an oncological emergency and affects up to 5% of cancer patients. Extradural compression accounts for the majority of cases, usually due to vertebral body metastases. It is more common in patients with lung, breast and prostate cancer

Features

- back pain - the earliest and most common symptom - may be worse on lying down and coughing
- lower limb weakness
- sensory changes: sensory loss and numbness
- neurological signs depend on the level of the lesion. Lesions above L1 usually result in upper motor neuron signs in the legs and a sensory level. Lesions below L1 usually cause lower motor neuron signs in the legs and perianal numbness. Tendon reflexes tend to be increased below the level of the lesion and absent at the level of the lesion

Management

- high-dose oral dexamethasone
- urgent oncological assessment for consideration of radiotherapy or surgery

Next question >

Myelofibrosis	21%
Burkitt's lymphoma	15%
Hairy cell leukaemia	36%
Acute myeloid leukaemia	16%

Interferons (IFN) are cytokines released by the body in response to viral infections and neoplasia. They are classified according to cellular origin and the type of receptor they bind to. IFN-alpha and IFN-beta bind to type 1 receptors whilst IFN-gamma binds only to type 2 receptors.

IFN-alpha is produced by leucocytes and has an antiviral action. It has been shown to be useful in the management of hepatitis B & C, Kaposi's sarcoma, metastatic renal cell cancer and hairy cell leukaemia



Next question >

Hairy cell leukaemia

Hairy cell leukaemia is a rare malignant proliferation disorder of B cells. It is more common in males (4:1)

Features

- pancytopenia
- splenomegaly
- skin vasculitis in 1/3 patients
- 'dry tap' despite bone marrow hypercellularity
- tartrate resistant acid phosphatase (TRAP) stain positive

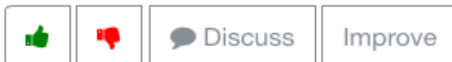
Management

- chemotherapy is first-line: cladribine, pentostatin
- immunotherapy is second-line: rituximab, interferon-alpha

Antithrombin III deficiency 5%

Antiphospholipid syndrome 77%

Antiphospholipid antibodies (aPL) are present in 15% of women with recurrent miscarriage, but in comparison, the prevalence of aPL in women with a low risk obstetric history is less than 2%



Next question >

Antiphospholipid syndrome: pregnancy

Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia. It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE)

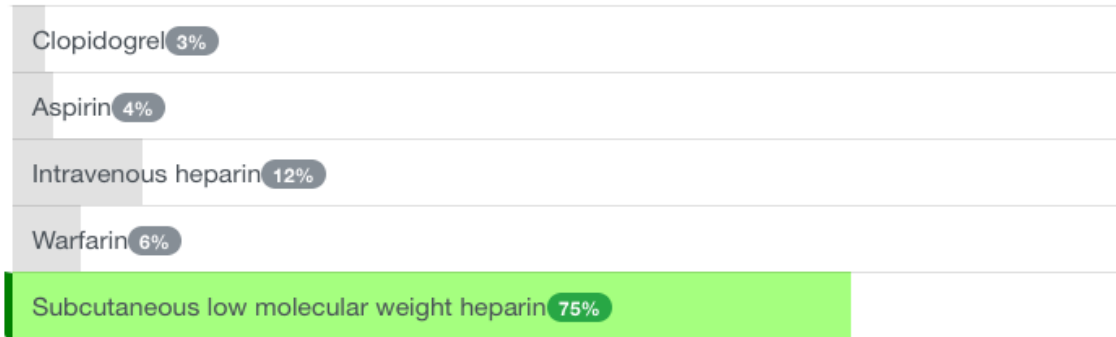
In pregnancy the following complications may occur:

- recurrent miscarriage
- IUGR
- pre-eclampsia
- placental abruption
- pre-term delivery
- venous thromboembolism

Management

- low-dose aspirin should be commenced once the pregnancy is confirmed on urine testing
- low molecular weight heparin once a fetal heart is seen on ultrasound. This is usually discontinued at 34 weeks gestation
- these interventions increase the live birth rate seven-fold

Next question >



Although teratogenic effects of warfarin are greater in the first trimester most clinicians would use low molecular weight heparin in this situation. Another factor to consider is the risk of peripartum haemorrhage and potential problems reversing the effects of warfarin if this occurred



Next question >

Pregnancy: DVT/PE

Overview

- pregnancy is a hypercoagulable state
- majority occur in last trimester

Pathophysiology

- increase in factors VII, VIII, X and fibrinogen
- decrease in protein S
- uterus presses on IVC causing venous stasis in legs

Management

- warfarin contraindicated
- S/C low-molecular weight heparin preferred to IV heparin (less bleeding and thrombocytopenia)

Next question >

Methaemoglobinaemia

Methaemoglobinaemia describes haemoglobin which has been oxidised from Fe^{2+} to Fe^{3+} . This is normally regulated by NADH methaemoglobin reductase, which transfers electrons from NADH to methaemoglobin resulting in the reduction of methaemoglobin to haemoglobin. There is tissue hypoxia as Fe^{3+} cannot bind oxygen, and hence the oxidation dissociation curve is moved to the left

Congenital causes

- haemoglobin chain variants: HbM, HbH
- NADH methaemoglobin reductase deficiency

Acquired causes

- drugs: sulphonamides, nitrates, dapsone, sodium nitroprusside, primaquine
- chemicals: aniline dyes

Features

- 'chocolate' cyanosis
- dyspnoea, anxiety, headache
- severe: acidosis, arrhythmias, seizures, coma
- normal pO_2 but decreased oxygen saturation

Management

- NADH - methaemoglobinaemia reductase deficiency: ascorbic acid
- IV methylene blue if acquired

Next question >

B *I* 

A ▾ ▾ ▾ ▾ ▾

Burkitt's lymphoma is associated with which one of the following genetic changes:

Cyclin D1-IGH gene translocation	5%
TEL-JAK2 gene translocation	6%
Bcl-2 gene translocation	12%
C-myc gene translocation	69%
BCR-Abl1 gene translocation	9%

Burkitt's lymphoma - c-myc gene translocation



Next question >

Burkitt's lymphoma

Burkitt's lymphoma is a high-grade B-cell neoplasm. There are two major forms:

- endemic (African) form: typically involves maxilla or mandible
- sporadic form: abdominal (e.g. ileo-caecal) tumours are the most common form. More common in patients with HIV

Burkitt's lymphoma is associated with the c-myc gene translocation, usually t(8:14). The Epstein-Barr virus (EBV) is strongly implicated in the development of the African form of Burkitt's lymphoma and to a lesser extent the sporadic form.

Microscopy findings

- 'starry sky' appearance: lymphocyte sheets interspersed with macrophages containing dead apoptotic tumour cells

Blood product transfusion complications

Complications

- haemolytic: immediate or delayed
- febrile reactions
- transmission of viruses, bacteria, parasites, vCJD
- hyperkalaemia
- iron overload
- ARDS
- clotting abnormalities

Immediate haemolytic reaction

- e.g. ABO mismatch
- massive intravascular haemolysis

Febrile reactions

- due to white blood cell HLA antibodies
- often the result of sensitization by previous pregnancies or transfusions

Causes a degree of immunosuppression

- e.g. patients with colorectal cancer who have blood transfusions have a worse outcome than those who do not

Transmission of vCJD

- although the absolute risk is very small, vCJD may be transmitted via blood transfusion
- a number of steps have been taken to minimise this risk, including:
 - → from late 1999 onward, all donations have undergone removal of white cells (leucodepletion) in order to reduce any vCJD infectivity present
 - → from 1999, plasma derivatives have been fractionated from imported plasma rather than being sourced from UK donors. Fresh Frozen Plasma (FFP) used for children and certain groups of adults needing frequent transfusions is also imported
 - → from 2004 onward, recipients of blood components have been excluded from donating blood

Next question >

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associated with a good prognostic outcome in ALL, The t(1:19) translocation is associated with low levels of resistance to chemotherapy intervention in ALL, and thus a good prognostic outcome. The t(9:22) or Philadelphia translocation, is associated with a poor prognosis.

Precursor B-ALL is more responsive to chemotherapy than that involving more mature B lymphocytes.

   Discuss  Improve

Next question >

Acute lymphoblastic leukaemia: prognostic features

Good prognostic factors

- French-American-British (FAB) L1 type
- common ALL
- pre-B phenotype
- low initial WBC
- del(9p)

Poor prognostic factors

- FAB L3 type
- T or B cell surface markers
- Philadelphia translocation, t(9;22)
- age < 2 years or > 10 years
- male sex
- CNS involvement
- high initial WBC (e.g. > 100 * 10⁹/l)
- non-Caucasian

Next question >

B *I* 

A    

Burkitt's lymphoma is associated with a mutation in which one of the following genes?

Cyclin D1 gene	6%
PML gene	5%
BCR-ABL gene	10%
RAR-alpha gene	6%
MYC gene	73%

  [Discuss \(1\)](#) [Improve](#)

[Next question >](#)

Haematological malignancies: genetics

Below is a brief summary of the common translocations associated with haematological malignancies

t(9;22) - Philadelphia chromosome

- present in > 95% of patients with CML
- this results in part of the Abelson proto-oncogene being moved to the BCR gene on chromosome 22
- the resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal
- poor prognostic indicator in ALL

t(15;17)

- seen in acute promyelocytic leukaemia (M3)
- fusion of PML and RAR-alpha genes

Vitamin B12 deficiency

Vitamin B12 is mainly used in the body for red blood cell development and also maintenance of the nervous system. It is absorbed after binding to intrinsic factor (secreted from parietal cells in the stomach) and is actively absorbed in the terminal ileum. A small amount of vitamin B12 is passively absorbed without being bound to intrinsic factor.

Causes of vitamin B12 deficiency

- pernicious anaemia
- post gastrectomy
- poor diet
- disorders of terminal ileum (site of absorption): Crohn's, blind-loop etc
- metformin (rare)

Features of vitamin B12 deficiency

- macrocytic anaemia
- sore tongue and mouth
- neurological symptoms: e.g. Ataxia
- neuropsychiatric symptoms: e.g. Mood disturbances

Management

- if no neurological involvement 1 mg of IM hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months
- if a patient is also deficient in folic acid then it is important to treat the B12 deficiency first to avoid precipitating subacute combined degeneration of the cord

Next question >

B *I* 

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What would be the most appropriate next set of investigations?

Folate levels and anti-gastric parietal cell antibodies	66%
Schilling test	16%
Iron studies	6%
Folate levels and LDH	8%
Colonoscopy	4%

This patient has a macrocytic anaemia due to B12 deficiency demonstrated by the low B12 levels and hypersegmented polymorphs on blood film. The next step is to identify the cause of the B12 deficiency by investigating for pernicious anaemia and checking folate levels (combined B12 and folate deficiency are common). Anti-gastric parietal cell antibodies are present in 90% patients with PA (but also 5-10% patients without PA). Other tests for PA are anti-intrinsic factor antibodies which are more specific but less sensitive than anti-parietal cell antibodies (present in 50%). In the past, Schilling tests using radioisotope labelled B12 were used.

Explanation for other options:

- 2. Schilling test no longer used in clinical practice due to shortage of B12 radioisotope and less invasive means of testing available
- 3. Folate levels are useful and LDH would be raised in pernicious anaemia but this is a non-specific finding and does not aid diagnosis
- 4. Colonoscopy not indicated at this stage and would be more useful in a microcytic anaemia when GI blood loss would be a possible cause
- 5. This patient has a macrocytic rather than microcytic anaemia (which would fit with iron deficiency)



Next question >

Vitamin B12 deficiency

ITP - give oral prednisolone

The likely diagnosis in this patient is idiopathic thrombocytopenic purpura. The first line treatment in such patients is high-dose prednisolone. Bone marrow examination would demonstrate increased megakaryocytes



Next question >

ITP: investigation and management

Idiopathic thrombocytopenic purpura (ITP) is an immune mediated reduction in the platelet count. Antibodies are directed against the glycoprotein IIb-IIIa or Ib complex

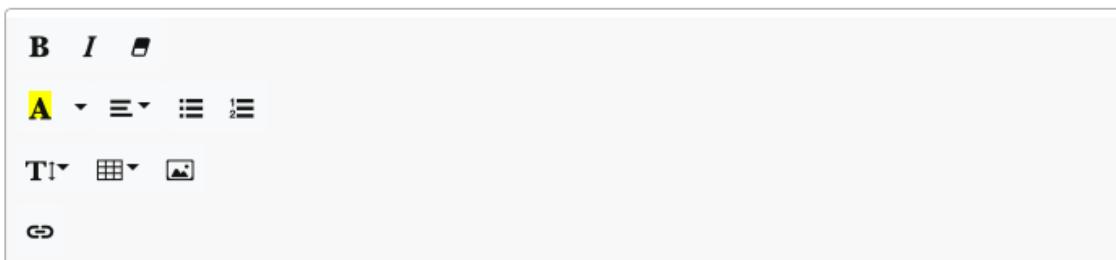
Investigations

- antiplatelet autoantibodies (usually IgG)
- bone marrow aspiration shows megakaryocytes in the marrow. This should be carried out prior to the commencement of steroids in order to rule out leukaemia

Management

- oral prednisolone (80% of patients respond)
- splenectomy if platelets < 30 after 3 months of steroid therapy
- IV immunoglobulins
- immunosuppressive drugs e.g. cyclophosphamide

Next question >



Two or more lymph nodes on the same side of the diaphragm with pruritus	5%
Nodes on both sides of diaphragm with night sweats	63%
Two or more lymph nodes on the same side of the diaphragm with night sweats	18%
Two or more lymph nodes on the same side of the diaphragm with no systemic symptoms	6%

Discuss Improve

Next question >

Hodgkin's lymphoma: staging

Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterised by the presence of the Reed-Sternberg cell. It has a bimodal age distributions being most common in the third and seventh decades

Ann-Arbor staging of Hodgkin's lymphoma

- I: single lymph node
- II: 2 or more lymph nodes/regions on same side of diaphragm
- III: nodes on both sides of diaphragm
- IV: spread beyond lymph nodes

Each stage may be subdivided into A or B

- A = no systemic symptoms other than pruritus
- B = weight loss > 10% in last 6 months, fever > 38c, night sweats (poor prognosis)

Next question >

B *I*

accurately describes the management of this patient?

Bronchodilators are indicated	6%
The patient should undergo a simple transfusion to a target Hb > 8g/L	16%
The patient should undergo an exchange transfusion to a target Hb > 8g/L	37%
Incentive spirometry is indicated	30%
Empirical antibiotic therapy is not indicated	11%

This question requires the candidate first of all to diagnose this presentation as an acute chest syndrome. The British Committee for Standards in Haematology (BCSH) defines this as 'an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray'.

The fundamentals of initial management are as follows:

- Oxygen therapy to maintain saturations > 95%
- Intravenous fluids to ensure euvolaemia
- Adequate pain relief
- Incentive spirometry in all patients presenting with rib or chest pain
- Antibiotics with cover for atypical organisms
- Early consultation with the critical care team and haematology

A senior haematologist will make a decision as to whether a simple or exchange transfusion is necessary, and guidelines suggest an Hb target of 100-110g/L in either instance. On presentation, patients with acute chest syndrome should be fully cross matched and a history of red cell antibodies sought.

Bronchodilators are indicated if asthma co-exists with acute chest syndrome, or if there is evidence of acute bronchospasm on auscultation.

Discuss (1)

Improve

Next question >

Sickle-cell crises

Sickle cell anaemia is characterised by periods of good health with intervening crises

Four main types of crises are recognised:

- thrombotic, 'painful crises'
- sequestration
- aplastic
- haemolytic

Thrombotic crises

- also known as painful crises or vaso-occlusive crises
- precipitated by infection, dehydration, deoxygenation
- infarcts occur in various organs including the bones (e.g. avascular necrosis of hip, hand-foot syndrome in children, lungs, spleen and brain)

Sequestration crises

- sickling within organs such as the spleen or lungs causes pooling of blood with worsening of the anaemia
- acute chest syndrome: dyspnoea, chest pain, pulmonary infiltrates, low pO₂ - the most common cause of death after childhood

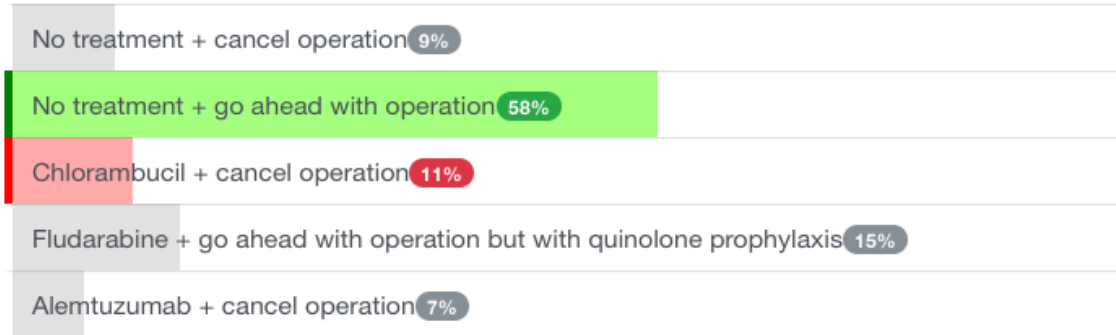
Aplastic crises

- caused by infection with parvovirus
- sudden fall in haemoglobin

Haemolytic crises

- rare
- fall in haemoglobin due an increased rate of haemolysis

Next question >



There is no indication for treating this patient at the current time or not going ahead with surgery



Next question >

Chronic lymphocytic leukaemia: management

Indications for treatment

- progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia
- massive (>10 cm) or progressive lymphadenopathy
- massive (>6 cm) or progressive splenomegaly
- progressive lymphocytosis: > 50% increase over 2 months or lymphocyte doubling time < 6 months
- systemic symptoms: weight loss > 10% in previous 6 months, fever >38°C for > 2 weeks, extreme fatigue, night sweats
- autoimmune cytopaenias e.g. ITP

Management

- patients who have no indications for treatment are monitored with regular blood counts
- fludarabine, cyclophosphamide and rituximab (FCR) has now emerged as the initial treatment of choice for the majority of patients

Next question >



 Discuss (1) Improve

Next question >

IgG4-related disease

IgG4-related disease has been described in virtually every organ system: the biliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium, and skin. The histopathological features are similar across organs, regardless of the site. IgG4-related disease is analogous to sarcoidosis, in which diverse organ manifestations are linked by similar histopathological characteristics. Raised concentrations of IgG4 in tissue and serum can be helpful in diagnosing IgG4 disease, but neither is a specific diagnostic marker.

Examples include:

- Riedel's Thyroiditis
- Autoimmune pancreatitis
- Mediastinal and Retroperitoneal Fibrosis
- Periaortitis/periarteritis/Inflammatory aortic aneurysm
- Kuttner's Tumour (submandibular glands) & Mikulicz Syndrome (salivary and lacrimal glands)
- Possibly sjogren's and primary biliary cirrhosis

Next question >

B *I* 
A ▾ ▮ ▮ ▮ ▮
T ▾ ▮ ▮ ▮ ▮


Which one of the following features is least associated with Waldenstrom's macroglobulinaemia?

Cryoglobulinaemia	18%
Bone pain	41%
Retinal vein thrombosis	15%
Hepatosplenomegaly	12%
Monoclonal IgM paraproteinaemia	14%

  [Discuss](#) [Improve](#)

[Next question >](#)

Waldenstrom's macroglobulinaemia

Waldenstrom's macroglobulinaemia is an uncommon condition seen in older men. It is a lymphoplasmacytoid malignancy characterised by the secretion of a monoclonal IgM paraprotein

Features

- monoclonal IgM paraproteinaemia
- systemic upset: weight loss, lethargy
- hyperviscosity syndrome e.g. visual disturbance
- hepatosplenomegaly
- lymphadenopathy
- cryoglobulinaemia e.g. Raynaud's

[Next question >](#)

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Questions

Female sex 8%

Philadelphia chromosome positive 63%

Philadelphia translocation, t(9;22) - good prognosis in CML, poor prognosis in AML + ALL

Discuss Improve

Next question >

Acute lymphoblastic leukaemia: prognostic features

Good prognostic factors

- French-American-British (FAB) L1 type
- common ALL
- pre-B phenotype
- low initial WBC
- del(9p)

Poor prognostic factors

- FAB L3 type
- T or B cell surface markers
- Philadelphia translocation, t(9;22)
- age < 2 years or > 10 years
- male sex
- CNS involvement
- high initial WBC (e.g. > 100 * 10⁹/l)
- non-Caucasian

Next question >

B I



Blood product transfusion complications

Complications

- haemolytic: immediate or delayed
- febrile reactions
- transmission of viruses, bacteria, parasites, vCJD
- hyperkalaemia
- iron overload
- ARDS
- clotting abnormalities

Immediate haemolytic reaction

- e.g. ABO mismatch
- massive intravascular haemolysis

Febrile reactions

- due to white blood cell HLA antibodies
- often the result of sensitization by previous pregnancies or transfusions

Causes a degree of immunosuppression

- e.g. patients with colorectal cancer who have blood transfusions have a worse outcome than those who do not

Transmission of vCJD

- although the absolute risk is very small, vCJD may be transmitted via blood transfusion
- a number of steps have been taken to minimise this risk, including:
 - → from late 1999 onward, all donations have undergone removal of white cells (leucodepletion) in order to reduce any vCJD infectivity present
 - → from 1999, plasma derivatives have been fractionated from imported plasma rather than being sourced from UK donors. Fresh Frozen Plasma (FFP) used for children and certain groups of adults needing frequent transfusions is also imported
 - → from 2004 onward, recipients of blood components have been excluded from donating blood

[Next question >](#)

Blood products: FFP, cryoprecipitate and prothrombin complex

NICE published guidelines on the use of blood products in 2015.

Fresh frozen plasma (FFP)

- most suited for 'clinically significant' but without 'major haemorrhage' in patients with a prothrombin time (PT) ratio or activated partial thromboplastin time (APTT) ratio > 1.5
- typically 150-220 mL
- can be used prophylactically in patients undergoing invasive surgery where there is a risk of significant bleeding

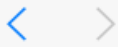
Cryoprecipitate

- contains concentrated Factor VIII:C, von Willebrand factor, fibrinogen, Factor XIII and fibronectin, produced by further processing of Fresh Frozen Plasma (FFP). Clinically it is most commonly used to replace fibrinogen
- much smaller volume than FFP, typically 15-20mL
- most suited for patients for 'clinically significant' but without 'major haemorrhage' who have a fibrinogen concentration < 1.5 g/L
- example use cases include disseminated intravascular coagulation, liver failure and hypofibrinogenaemia secondary to massive transfusion. It may also be used in an emergency situation for haemophiliacs (when specific factors not available) and in von Willebrand disease
- can be used prophylactically in patients undergoing invasive surgery where there is a risk of significant bleeding where the fibrinogen concentration < 1.0 g/L

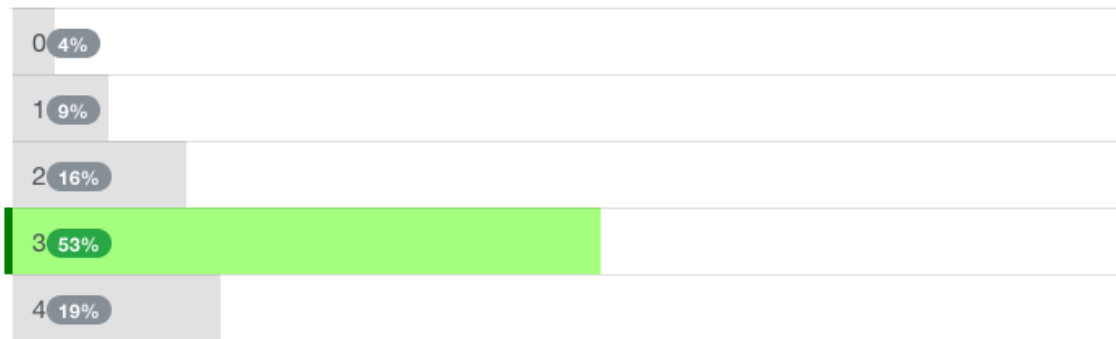
Prothrombin complex concentrate

- used for the emergency reversal of anticoagulation in patients with either severe bleeding or a head injury with suspected intracerebral haemorrhage
- can be used prophylactically in patients undergoing emergency surgery depending on the particular circumstance

Next question >



A 75-year-old male patient has metastatic colorectal cancer. He spends most of his day resting in bed or in his chair and requires assistance with his activities of daily living. What is his Eastern Cooperative Oncology Group (ECOG) score?



Discuss

Improve

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ECOG score

The ECOG score is a 'performance status' scale, or a score that measures the functional status a patient. It is used to decide if a patient is a good or poor candidate for future oncological therapies.

Those with a poor functional status is a poor candidate for further chemotherapy.

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead



Next question >

Leukaemoid reaction

The leukaemoid reaction describes the presence of immature cells such as myeloblasts, promyelocytes and nucleated red cells in the peripheral blood. This may be due to infiltration of the bone marrow causing the immature cells to be 'pushed out' or sudden demand for new cells

Causes

- severe infection
- severe haemolysis
- massive haemorrhage
- metastatic cancer with bone marrow infiltration

A relatively common clinical problem is differentiating chronic myeloid leukaemia from a leukaemoid reaction. The following differences may help:

Leukaemoid reaction

- high leucocyte alkaline phosphatase score
- toxic granulation (Dohle bodies) in the white cells
- 'left shift' of neutrophils i.e. three or less segments of the nucleus

Chronic myeloid leukaemia

- low leucocyte alkaline phosphatase score

Next question >

B *I*

A ▾ ≡ ≡ ≡

Which one of the following therapeutic options is least recognised in the treatment of aplastic anaemia?

Interferon-alpha	37%
Stem cell transplantation	7%
Anti-lymphocyte globulin	17%
Anti-thymocyte globulin	19%
Platelet transfusion	19%

  Discuss (1) Improve

Next question >

Aplastic anaemia: management

Supportive

- blood products
- prevention and treatment of infection

Anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG)

- prepared in animals (e.g. rabbits or horses) by injecting human lymphocytes
- is highly allergenic and may cause serum sickness (fever, rash, arthralgia), therefore steroid cover usually given
- immunosuppression using agents such as ciclosporin may also be given

Stem cell transplantation

- allogeneic transplants have a success rate of up to 80%

Next question >

What is the most useful marker of prognosis in myeloma?

Calcium level	16%
Urine Bence-Jones protein levels	15%
Alkaline phosphatase	10%
ESR	8%
B2-microglobulin	50%

  Discuss (1) Improve

Next question >

Myeloma: prognosis

B2-microglobulin is a useful marker of prognosis - raised levels imply poor prognosis. Low levels of albumin are also associated with a poor prognosis

International prognostic index

Stage	Criteria	Median survival (months)
I	B2 microglobulin < 3.5 mg/l Albumin > 35 g/l	62
II	Not I or III	45
III	B2 microglobulin > 5.5 mg/l	29

Next question >



Each one of the following is associated with hyposplenism, except:

Sickle-cell anaemia	17%
Liver cirrhosis	45%
Systemic lupus erythematosus	19%
Coeliac disease	12%
Splenectomy	7%



Discuss

Improve

[Next question >](#)

Hyposplenism

Causes

- splenectomy
- sickle-cell
- coeliac disease, dermatitis herpetiformis
- Graves' disease
- systemic lupus erythematosus
- amyloid

Features

- Howell-Jolly bodies
- siderocytes

[Next question >](#)

Chronic lymphocytic leukaemia	15%
Myelofibrosis	16%
Polycythaemia rubra vera	14%
Haemophilia A	7%
Acute myeloid leukaemia	48%

Gingival hyperplasia: phenytoin, ciclosporin, calcium channel blockers and AML

Discuss

Improve

Next question >

Gingival hyperplasia

Drug causes of gingival hyperplasia

- phenytoin
- ciclosporin
- calcium channel blockers (especially nifedipine)

Other causes of gingival hyperplasia include

- acute myeloid leukaemia (myelomonocytic and monocytic types)

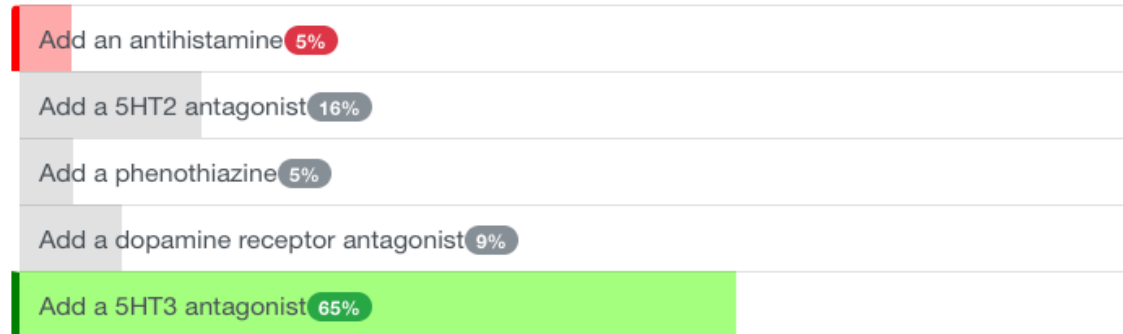
Next question >

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A 54-year-old female is receiving a course of chemotherapy for breast cancer. She is experiencing troublesome vomiting which has not been helped by domperidone. What is the most appropriate next management step?



Next question >

Chemotherapy side-effects: nausea and vomiting

Nausea and vomiting are common side-effects of chemotherapy. Risk factors for the development of symptoms include:

- anxiety
- age less than 50 years old
- concurrent use of opioids
- the type of chemotherapy used

For patients at low-risk of symptoms then drugs such as metoclopramide may be used first-line. For high-risk patients then 5HT3 receptor antagonists such as ondansetron are often effective, especially if combined with dexamethasone

Next question >

Next question >

Neutropenic sepsis

Neutropenic sepsis is a relatively common complication of cancer therapy, usually as a consequence of chemotherapy. It may be defined as a neutrophil count of $< 0.5 \times 10^9$ in a patient who is having anticancer treatment and has one of the following:

- a temperature higher than 38°C or
- other signs or symptoms consistent with clinically significant sepsis

Prophylaxis

- if it is anticipated that patients are likely to have a neutrophil count of $< 0.5 \times 10^9$ as a consequence of their treatment they should be offered a fluoroquinolone

Management

- antibiotics must be started immediately, do not wait for the WBC
- NICE recommend starting empirical antibiotic therapy with piperacillin with tazobactam (Tazocin) immediately
- many units add vancomycin if the patient has central venous access but NICE do not support this approach
- following this initial treatment patients are usually assessed by a specialist and risk-stratified to see if they may be able to have outpatient treatment
- if patients are still febrile and unwell after 48 hours an alternative antibiotic such as meropenem is often prescribed +/- vancomycin
- if patients are not responding after 4-6 days the Christie guidelines suggest ordering investigations for fungal infections (e.g. HRCT), rather than just starting therapy antifungal therapy blindly
- there may be a role for G-CSF in selected patients

Next question >

B *I* 

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Next question >

Lymphadenopathy

There are many causes of generalised lymphadenopathy

Infective

- infectious mononucleosis
- HIV, including seroconversion illness
- eczema with secondary infection
- rubella
- toxoplasmosis
- CMV
- tuberculosis
- roseola infantum

Neoplastic

- leukaemia
- lymphoma

Others

- autoimmune conditions: SLE, rheumatoid arthritis
- graft versus host disease
- sarcoidosis
- drugs: phenytoin and to a lesser extent allopurinol, isoniazid

Next question >

B *I* 
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Methylprednisolone	16%
Ceftriaxone + vancomycin	7%
Plasma exchange	58%

TTP - plasma exchange is first-line

This patient has thrombotic thrombocytopenic purpura, a condition associated with pregnancy

  [Discuss \(3\)](#) [Improve](#)

[Next question >](#)

Thrombotic thrombocytopenic purpura: management

Pathogenesis of thrombotic thrombocytopenic purpura (TTP)

- abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels
- in TTP there is a deficiency of protease which breakdowns large multimers of von Willebrand's factor
- overlaps with haemolytic uraemic syndrome (HUS)

Management

- no antibiotics - may worsen outcome
- plasma exchange is the treatment of choice
- steroids, immunosuppressants
- vincristine

[Next question >](#)

B *I* 

A ▾ ≡ ≡ ≡

Next question >

Polycythaemia

Polycythaemia may be relative, primary (polycythaemia rubra vera) or secondary

Relative causes

- dehydration
- stress: Gaisbock syndrome

Primary

- polycythaemia rubra vera

Secondary causes

- COPD
- altitude
- obstructive sleep apnoea
- excessive erythropoietin: cerebellar haemangioma, hypernephroma, hepatoma, uterine fibroids*

To differentiate between true (primary or secondary) polycythaemia and relative polycythaemia red cell mass studies are sometimes used. In true polycythaemia the total red cell mass in males > 35 ml/kg and in women > 32 ml/kg

*uterine fibroids may cause menorrhagia which in turn leads to blood loss - polycythaemia is rarely a clinical problem

Next question >

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Next question >

Vitamin B12 deficiency

Vitamin B12 is mainly used in the body for red blood cell development and also maintenance of the nervous system. It is absorbed after binding to intrinsic factor (secreted from parietal cells in the stomach) and is actively absorbed in the terminal ileum. A small amount of vitamin B12 is passively absorbed without being bound to intrinsic factor.

Causes of vitamin B12 deficiency

- pernicious anaemia
- post gastrectomy
- poor diet
- disorders of terminal ileum (site of absorption): Crohn's, blind-loop etc
- metformin (rare)

Features of vitamin B12 deficiency

- macrocytic anaemia
- sore tongue and mouth
- neurological symptoms: e.g. Ataxia
- neuropsychiatric symptoms: e.g. Mood disturbances

Management

- if no neurological involvement 1 mg of IM hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months
- if a patient is also deficient in folic acid then it is important to treat the B12 deficiency first to avoid precipitating subacute combined degeneration of the cord

Next question >

B *I* 

Antiphospholipid syndrome in pregnancy: aspirin + LMWH

The ultrasound at 11 weeks gestation would show a fetal heart if the pregnancy was viable. This patient should therefore be taking both aspirin and low-molecular weight heparin.



Next question >

Antiphospholipid syndrome: pregnancy

Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia. It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE)

In pregnancy the following complications may occur:

- recurrent miscarriage
- IUGR
- pre-eclampsia
- placental abruption
- pre-term delivery
- venous thromboembolism

Management

- low-dose aspirin should be commenced once the pregnancy is confirmed on urine testing
- low molecular weight heparin once a fetal heart is seen on ultrasound. This is usually discontinued at 34 weeks gestation
- these interventions increase the live birth rate seven-fold

Next question >

Thrombocytosis

Thrombocytosis is an abnormally high platelet count, usually $> 400 \times 10^9/l$.

Causes of thrombocytosis

- reactive: platelets are an acute phase reactant - platelet count can increase in response to stress such as a severe infection or surgery
- malignancy
- essential thrombocytosis (see below), or as part of another myeloproliferative disorder such as chronic myeloid leukaemia or polycythaemia rubra vera
- hyposplenism

Essential thrombocytosis

Essential thrombocytosis is one of the myeloproliferative disorders which overlaps with chronic myeloid leukaemia, polycythaemia rubra vera and myelofibrosis. Megakaryocyte proliferation results in an overproduction of platelets.

Features

- platelet count $> 600 \times 10^9/l$
- both thrombosis (venous or arterial) and haemorrhage can be seen
- a characteristic symptom is a burning sensation in the hands
- a JAK2 mutation is found in around 50% of patients

Management

- hydroxyurea (hydroxycarbamide) is widely used to reduce the platelet count
- interferon- α is also used in younger patients
- low-dose aspirin may be used to reduce the thrombotic risk

Next question >

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passmedicine.com
Superior Vena Cava Syndrome, BMJ Best Practice, N.p., 20 July 2016
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Superior vena cava obstruction

Superior vena cava (SVC) obstruction is an oncological emergency caused by compression of the SVC. It is most commonly associated with lung cancer.

Features

- dyspnoea is the most common symptom
- swelling of the face, neck and arms - conjunctival and periorbital oedema may be seen
- headache
- visual disturbance
- pulseless jugular venous distension

Causes

- common malignancies: small cell lung cancer, lymphoma
- other malignancies: metastatic seminoma, Kaposi's sarcoma, breast cancer
- aortic aneurysm
- mediastinal fibrosis
- goitre
- SVC thrombosis

Management

- general: dexamethasone, balloon venoplasty, stenting
- small cell: chemotherapy + radiotherapy
- non-small cell: radiotherapy

Next question >

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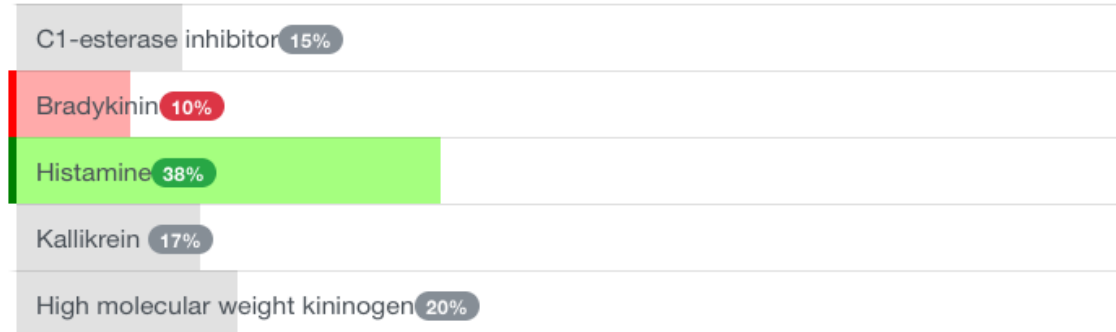


Which one of the following is not implicated in the pathogenesis of hereditary angioedema?



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Hereditary angioedema (HAE) is pathophysiologically separate from anaphylaxis and is treated differently. Therapeutic options are: intravenous infusion of human C1-esterase inhibitor or subcutaneous injection of the bradykinin receptor inhibitor icatibant

Hereditary angioedema (HAE) is an autosomal dominantly inherited immune condition characterised by episodic swelling of the extremities, intra-abdominal viscera and mucous membranes. Often attacks are unprecipitated although sometimes exogenous oestrogens in the form of contraception can be traced, as well as exposure to angiotensin-converting enzyme inhibitors. The primary pathophysiological defect is in the complement cascade and deficiencies in factors C4 and C1-esterase inhibitor are seen in type I. In type II HAE C1-esterase inhibitor levels are normal but the enzyme is dysfunctional and activity is low. An acquired form of HAE is described in which all complement levels are low. In type III HAE the clinical features of angioedema are present but immunological testing reveals normal levels and activity of complement factors. Ultimately, failure of C1-esterase inhibitor leads to upregulation of the rest of the complement system and membrane attack complex, but also it leads to activation of the signalling protein kallikrein which acts directly on the vascular wall to increase permeability, and it cleaves high molecular weight kininogen to release bradykinin, again a potent peripheral vasodilator giving rise to the symptoms of HAE.

HAE should be recognised as a separate entity from anaphylaxis since the clinical signs are different, as is the pathophysiology of the condition and its treatment. Anaphylaxis is an IgE mediated immune phenomenon related to a specific allergen causing massive mast cell degranulation and histamine release. HAE is driven by complement dysregulation and consequent release of the inflammatory cytokines bradykinin and kallikrein. Anaphylaxis is characterised by rapidly progressive, itchy, erythematous, oedematous rash, swelling of the lips, tongue and airways with accompanying hypovolaemic hypotension and cardiovascular collapse due to increased tissue permeability. Anaphylaxis is a medical emergency and death can ensue



degranulation and histamine release. HAE is driven by complement dysregulation and consequent release of the inflammatory cytokines bradykinin and kallikrein. Anaphylaxis is characterised by rapidly progressive, itchy, erythematous, oedematous rash, swelling of the lips, tongue and airways with accompanying hypovolaemic hypotension and cardiovascular collapse due to increased tissue permeability. Anaphylaxis is a medical emergency and death can ensue in minutes unless treated properly. HAE in comparison may present recurrently and often with no obvious precipitant. Usually, its course is more insidious with the evolution of symptoms over minutes to hours. Swelling will often only affect an isolated limb and it is not itchy or painful and minimally erythematous. Hypotension is rarely seen and cardiovascular instability is extremely unlikely. HAE can be fatal however if swelling of the upper airways causes obstruction, and in some cases, prophylactic intubation and mechanical ventilation may be appropriate. Since the driving mechanism is not histamine in HAE, steroids and antihistamines are of no value. Where there is no haemodynamic compromise, adrenaline is not warranted and may even worsen the situation due to increased plasma glucose load and risk of capillary rupture.

Knowledge of the cytokine cascade in HAE allows for knowledge of its management. Since the initiating pathophysiological hallmark is a deficiency or reduced effectiveness of C1-esterase inhibitor, exogenous administration of synthetic or reconstituted inhibitor should be effective.

National guidelines released in 2013 recommend treatment of episodes of HAE with the administration of reconstituted human C1-esterase inhibitor. In the UK two brands are available; either Cinryze which is dosed at 1000 unit administration or Berinert at 20 units/kg. Both are administered as slow intravenous infusions. Interestingly, a good clinical response is often seen to these drugs even in HAE type III where C1-esterase levels are normal.

An alternative to exogenous C1-esterase inhibitor is icatibant which is a specific antagonist at B2 bradykinin receptors in vascular smooth muscle. The 30mg dose may be repeated up to three times in 24 hours but a rapid resolution of symptoms is often seen. Many patients with HAE are supplied with their own icatibant autoinjectors for use in the pre-hospital setting at the onset of symptoms.

Ecallantide is a selective inactivator of the cytokine kallikrein. It is highly effective in the treatment of HAE in the United States but has no European licence at this current time.



Discuss (1)

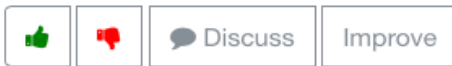
Improve

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t(15;22) 9%

t(17;22) 5%

Acute promyelocytic leukaemia - t(15;17)



Next question >

Acute promyelocytic leukaemia

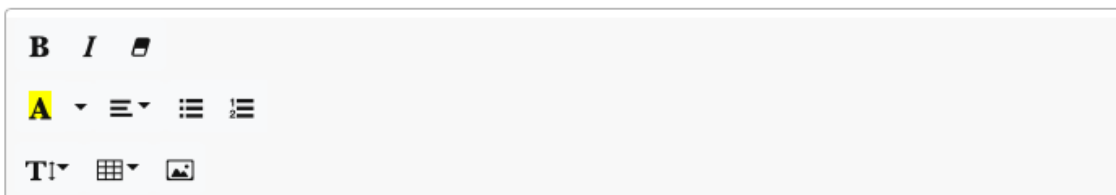
You are not normally expected to be able to differentiate the different subtypes of acute myeloid leukaemia (AML) for the MRCP. An exception to this is acute promyelocytic leukaemia (APML, the M3 subtype of AML). The importance of identifying APML lies in both the presentation (classically disseminated intravascular coagulation) and management

APML is associated with the t(15;17) translocation which causes fusion of the PML and RAR-alpha genes.

Features

- presents younger than other types of AML (average = 25 years old)
- DIC or thrombocytopenia often at presentation
- good prognosis

Next question >



A patient with lung cancer has a Positron Emission Tomography (PET) scan to evaluate possible metastatic disease. What does this type of scan demonstrate?



  Discuss (1) Improve

Next question >

Positron Emission Tomography (PET)

Positron Emission Tomography (PET) is a form of nuclear imaging which uses fluorodeoxyglucose (FDG) as the radiotracer. This allows a 3D image of metabolic activity to be generated using glucose uptake as a proxy marker. The images obtained are then combined with a conventional imaging technique such as CT to decide whether lesions are metabolically active.

Uses

- evaluating primary and possible metastatic disease
- cardiac PET: not used mainstream currently

Next question >

B I

Antithrombin III deficiency

Antithrombin III deficiency is an inherited cause of thrombophilia occurring in approximately 1:3,000 of the population. Inheritance is autosomal dominant

Antithrombin III inhibits several clotting factors, primarily thrombin, factor X and factor IX. It mediates the effects of heparin

Antithrombin III deficiency comprises a heterogeneous group of disorders, with some patients having a deficiency of normal antithrombin III whilst others produce abnormal antithrombin III

Features

- recurrent venous thromboses
- arterial thromboses do occur but are uncommon

Management

- thromboembolic events are treated with lifelong warfarinisation
- heparinisation during pregnancy*
- antithrombin III concentrates (often used during surgery or childbirth)

The table below shows the prevalence and relative risk of venous thromboembolism (VTE) of the different inherited thrombophilias:

Condition	Prevalence	Relative risk of VTE
Factor V Leiden (heterozygous)	5%	4
Prothrombin gene mutation (heterozygous)	1.5%	3
Protein C deficiency	0.3%	10
Protein S deficiency	0.1%	5-10
Antithrombin III deficiency	0.03	10-20

The answer is leukemoid reaction. Leucocyte ALP is one of types of alkaline phosphatase. It has a diagnostic value in differentiating causes of high number of white blood cells, seen on manual differentials.

The leukemoid reaction refers to the 'left-shift' of immature white blood cells that occurs in underlying infections. On a blood film, this could mistakenly be thought to be a malignant process (like CML). Leukocyte ALP can differentiate the two - a low score indicates undeveloped leukocytes, like those found in CML and AML. PNH also causes a low score.

Placental ALP found in pregnancy is a distractor.



Next question >

Leucocyte alkaline phosphatase

Raised in

- myelofibrosis
- leukaemoid reactions
- polycythaemia rubra vera
- infections
- steroids, Cushing's syndrome
- pregnancy, oral contraceptive pill

Low in

- chronic myeloid leukaemia
- pernicious anaemia
- paroxysmal nocturnal haemoglobinuria
- infectious mononucleosis

Next question >

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*as patients with antithrombin III deficiency have a degree of resistance to heparin anti-Xa levels should be monitored carefully to ensure adequate anticoagulation

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[Next question >](#)

Leucocyte alkaline phosphatase

Raised in

- myelofibrosis
- leukaemoid reactions
- polycythaemia rubra vera
- infections
- steroids, Cushing's syndrome
- pregnancy, oral contraceptive pill

Low in

- chronic myeloid leukaemia
- pernicious anaemia
- paroxysmal nocturnal haemoglobinuria
- infectious mononucleosis

[Next question >](#)**B***I***A****T**



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Next question >

Protein C deficiency

Protein C deficiency is an autosomal codominant condition which causes an increased risk of thrombosis

Features

- venous thromboembolism
- skin necrosis following the commencement of warfarin: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis

Next question >

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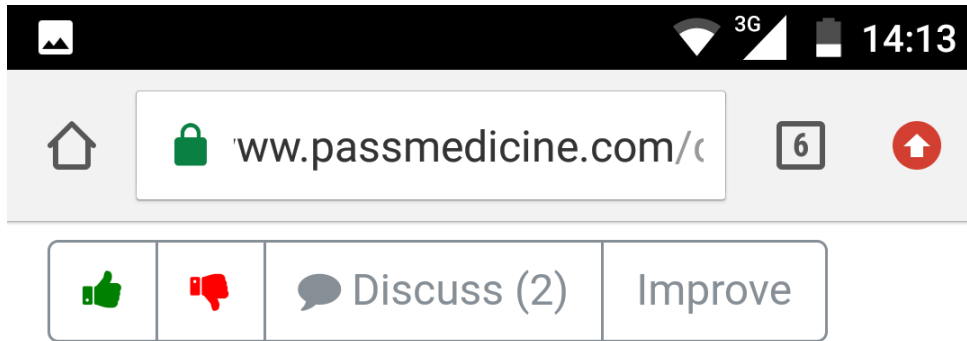


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Next question >

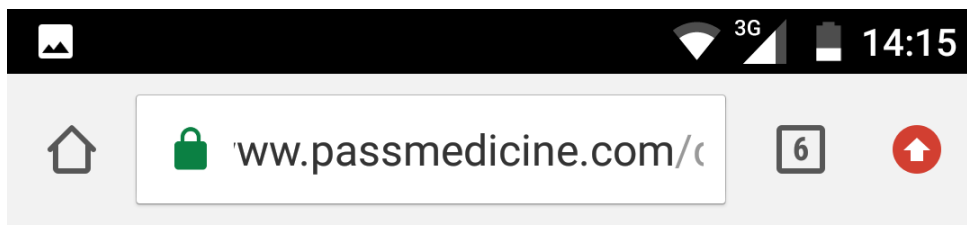
Drug-induced pancytopenia

Drug causes of pancytopenia

- cytotoxics
- antibiotics: trimethoprim, chloramphenicol
- anti-rheumatoid: gold, penicillamine
- carbimazole*
- anti-epileptics: carbamazepine
- sulphonylureas: tolbutamide

*causes both agranulocytosis and pancytopenia

Next question >



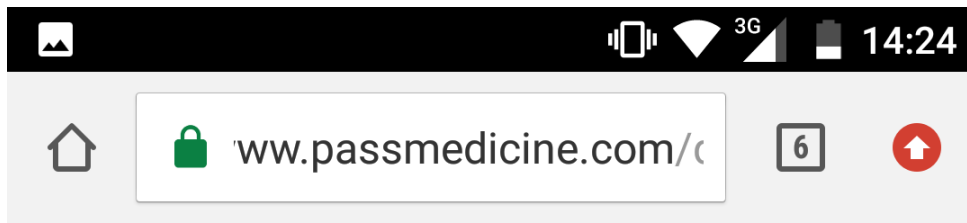
A 39-year-old woman presents with a strange collection of symptoms over the past six months. She has been seen by multiple specialists, none of whom have been able to find a cause for her symptoms.

Her symptoms include worsening headaches, memory loss, low mood, lethargy, abdominal pain causing paroxysms of intermittent generalised pain, nausea, an unusual taste in her mouth and paraesthesia in her extremities.

She is irritable during your consultation and at times tearful complaining that no one is taking her seriously and confiding that her General Practitioner had referred her for counselling.

Routine blood tests show:

Hb	101g/L
WBC	5.6 10^9 /L
Platelets	350 10^9 /L
MCV	77fL



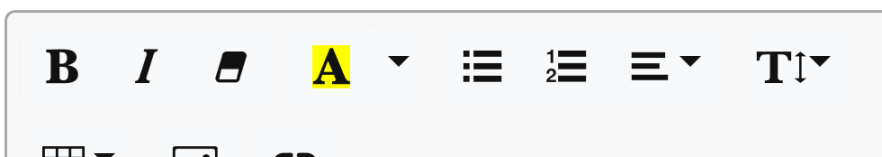
Beta-thalassaemia trait

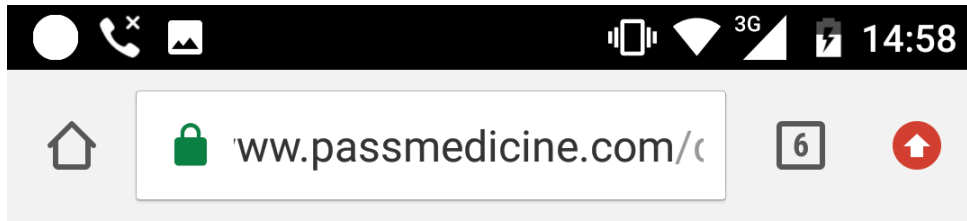
The thalassaemias are a group of genetic disorders characterised by a reduced production rate of either alpha or beta chains. Beta-thalassaemia trait is an autosomal recessive condition characterised by a mild hypochromic, microcytic anaemia. It is usually asymptomatic

Features

- mild hypochromic, microcytic anaemia - microcytosis is characteristically disproportionate to the anaemia
- HbA2 raised (> 3.5%)

Next question >





Acute intermittent porphyria (AIP)

- autosomal dominant
- defect in porphobilinogen deaminase
- female and 20-40 year olds more likely to be affected
- typically present with abdominal symptoms, neuropsychiatric symptoms
- hypertension and tachycardia common
- urine turns deep red on standing

Porphyria cutanea tarda (PCT)

- most common hepatic porphyria
- defect in uroporphyrinogen decarboxylase
- may be caused by hepatocyte damage e.g. alcohol, oestrogens
- classically photosensitive rash with bullae, skin fragility on face and dorsal aspect of hands
- urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp

Porphyria cutanea tarda (PCT)

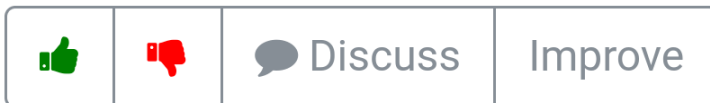
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- classically photosensitive rash with bullae, skin fragility on face and dorsal aspect of hands
- urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp
- manage with chloroquine

Variegate porphyria

- autosomal dominant
- defect in protoporphyrinogen oxidase
- photosensitive blistering rash
- abdominal and neurological symptoms
- more common in South Africans

Next question >

<https://pathways.nice.org.uk/pathways/metastatic-spinal-cord-compression#content=view-quality-statement%3Aquality-statements-imaging-and-treatment-plans-for-adults-with-suspected-spinal-metastases>



Next question >

Spinal metastases

Patients may present with spinal metastases before developing metastatic spinal cord compression. It is, therefore, important to detect these patients early before any neurological compromise develops.

Symptoms and findings

- Unrelenting lumbar back pain
- Any thoracic or cervical back pain
- Worse with sneezing, coughing or straining
- Nocturnal



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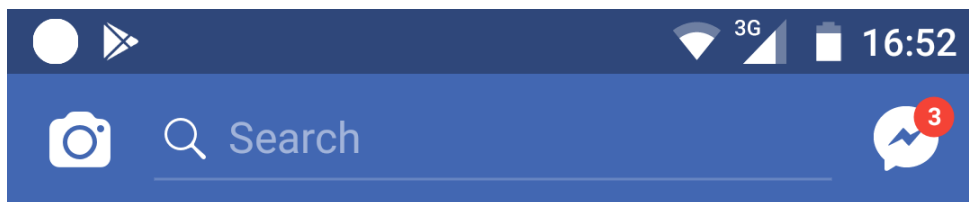
- Unrelenting lumbar back pain
- Any thoracic or cervical back pain
- Worse with sneezing, coughing or straining
- Nocturnal
- Associated with tenderness

If any neurological features are present then spinal cord compression must be suspected and acted on promptly. Without neurological features, a whole spine MRI should be completed within one week. The whole spine should be imaged as patients commonly present with multi-level disease.

Sources:

Al-Qurainy, Rasha, and Emily Collis. 'Metastatic Spinal Cord Compression: Diagnosis and Management.' Bmj (2016): l2539.

Metastatic Spinal Cord Compression in Adults: Risk Assessment, Diagnosis and Management Clinical Guideline [CG75]. National Institute of Clinical Excellence. N.p., Nov. 2008.



1 hr • 🌐

A 30-year-old man presents with painful, purple coloured lesions on his shins. Some of these lesions have started to heal and no evidence of scarring is seen. These have been present for the past 2 weeks. There is no past medical history of note and he takes no regular medications. What is the most useful next investigation?

- A. Liver function tests
- B. Anti-nuclear antibody
- C. ECG
- D. HIV test
- E. Chest x-ray



24

40 Comments



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Salim Raoof



5 hrs • 🌐



Venous thromboembolism: risk factors

Common predisposing factors include malignancy, pregnancy and the period following an operation. The comprehensive list below is partly based on the 2010 SIGN venous thromboembolism (VTE) guidelines:

General

- increased risk with advancing age
- obesity
- family history of VTE
- pregnancy (especially puerperium)
- immobility
- hospitalisation
- anaesthesia
- central venous catheter: femoral >> subclavian

Underlying conditions

- malignancy
- thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency
- heart failure

Underlying conditions

- malignancy
- thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency
- heart failure
- antiphospholipid syndrome
- Behcet's
- polycythaemia
- nephrotic syndrome
- sickle cell disease
- paroxysmal nocturnal haemoglobinuria
- hyperviscosity syndrome
- homocystinuria

Medication

- combined oral contraceptive pill: 3rd generation more than 2nd generation
- hormone replacement therapy: the risk of VTE is higher in women taking oestrogen + progestogen preparations compared to those taking oestrogen only preparations
- raloxifene and tamoxifen
- antipsychotics (especially olanzapine) have recently been shown to be a risk

hypermobility syndrome

- homocystinuria

Medication

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- raloxifene and tamoxifen
- antipsychotics (especially olanzapine) have recently been shown to be a risk factor

It should be remembered however that around 40% of patients diagnosed with a PE have no major risk factors.

Next question >

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12:49

t(9;22) - Philadelphia chromosome

- present in > 95% of patients with CML
- this results in part of the Abelson proto-oncogene being moved to the BCR gene on chromosome 22
- the resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal
- poor prognostic indicator in ALL

t(15;17)

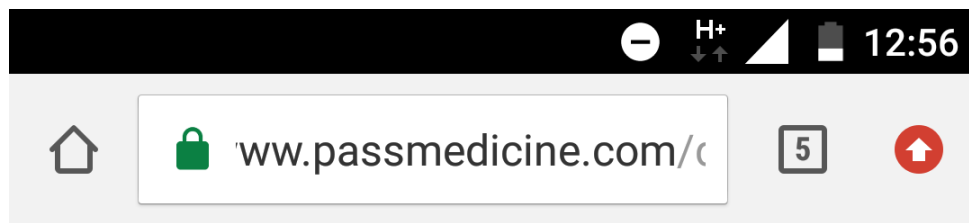
- seen in acute promyelocytic leukaemia (M3)
- fusion of PML and RAR-alpha genes

t(8;14)

- seen in Burkitt's lymphoma
- MYC oncogene is translocated to an immunoglobulin gene

t(11;14)

- Mantle cell lymphoma
- deregulation of the cyclin D1 (BCL-1) gene



Blood products: CMV negative and irradiated blood

Cytomegalovirus (CMV) is transmitted in leucocytes. As most blood products (except granulocyte transfusions) are now leucocyte depleted CMV negative products are rarely required.

Irradiated blood products are used to avoid transfusion graft versus host disease (TA-GVHD) caused by engraftment of viable donor T lymphocytes.

The table below shows the indications for CMV and irradiated blood:

Situation	CMV negative	Irradia
Granulocyte transfusions	✓	✓

Intra-uterine transfusions	✓	✓
Neonates up to 28 days post expected date of delivery	✓	✓
Pregnancy: Elective transfusions during pregnancy (not during labour or delivery)	✓	
Bone marrow / stem cell transplants		✓
Immunocompromised (e.g. chemotherapy or congenital)		✓
Patients with/previous Hodgkins Disease		✓
HIV		

A 17-year-old man is investigated after he bled excessively following a tooth extraction. The following results are obtained:

Plt	$173 \times 10^9/l$
PT	12.9 secs
APTT	84 secs

Which clotting factor is he most likely to be deficient in?

- ☐ Factor VI
- ☐ Factor VII
- ☐ Factor VIII
- ☒ Factor IX
- ☐ Factor X

Submit answer

Haloperidol may also be used





 Discuss (2)

Improve

Palliative care prescribing: hiccups

Management of hiccups

- chlorpromazine is licensed for the treatment of intractable hiccups
- haloperidol, gabapentin are also used
- dexamethasone is also used, particularly if there are hepatic lesions

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